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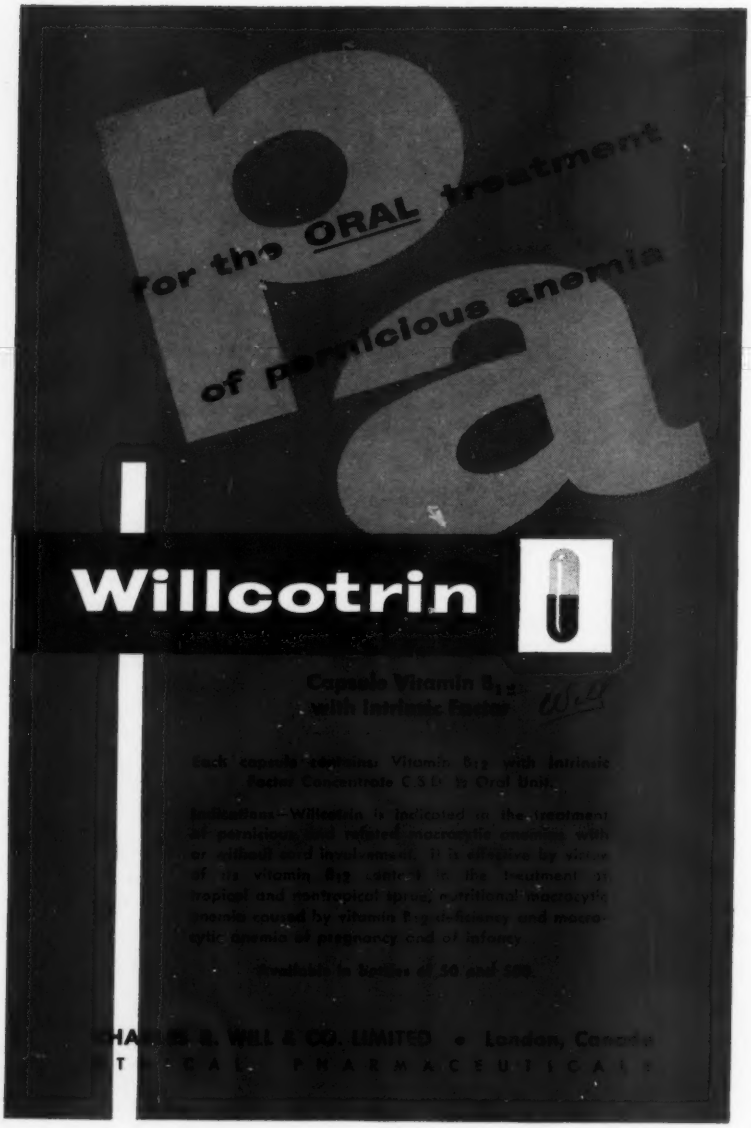

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Paediatrics

The Nephrotic Syndrome

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Definition:

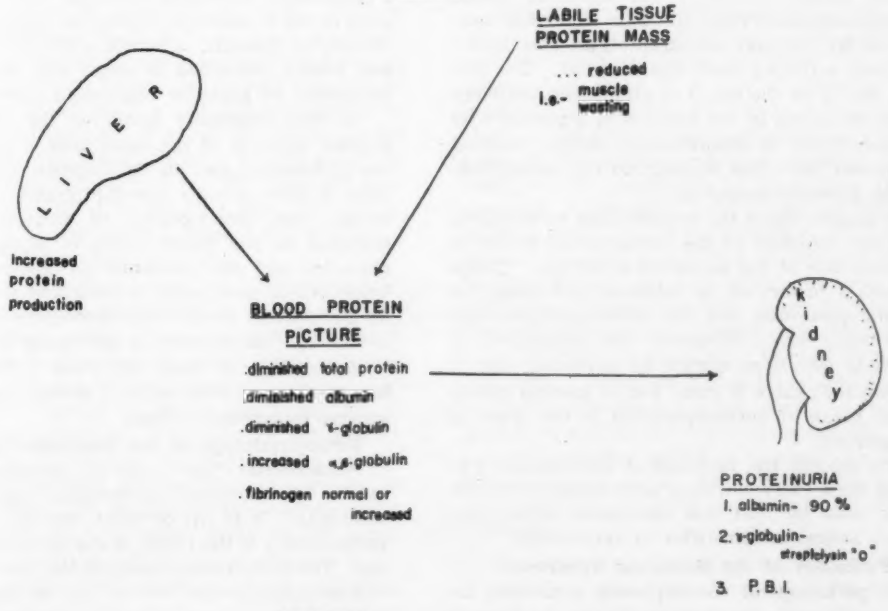
The nephronic syndrome may be defined as a symptom complex consisting of the following manifestations:

1. Edema
2. Proteinuria
3. Hypoproteinemia
4. Hyperlipemia.

Etiology of the Nephrotic Syndrome

This syndrome may be produced by many factors, some of which are known, and probably most of which are unknown. It may be considered as is epilepsy; a non-specific manifestation produced by many factors. An etiological classification of the nephrotic syndrome is set forth in Table I.

Table I



PROTEIN METABOLISM in the NEPHROTIC SYNDROME

Etiology of the Nephrotic Syndrome

1. Complications of Systemic Disease:
   a. diabetes mellitus—diabetic glomerulosclerosis
   b. amyloidosis
   c. lupus erythematosus
   d. syphilis
   e. typhus fever
   f. quartan malaria
   g. toxemia of pregnancy.
2. Glomerulonephritis: The nephrotic syndrome may occur in chronic glomerulonephritis (Ellis Type II, Subacute glomerulonephritis) (Boyd).
3. Chronic Pyelonephritis (rarely).
4. Bilateral Renal Vein Thrombosis.
5. Drugs and Toxins:
   a. tridione
   b. gold salts
   c. tetra ethylene melamine (tem)
   d. 6-mercaptopurine
   e. nitrogen mustard
   f. Cortisone
   g. bee stings
   h. poison oak.
6. Idiopathic — most cases.

Relationship of Glomerulonephritis and Nephrosis

In 1942 Professor A. Ellis reviewed the cases of glomerulonephritis in the London Hospital.[1] He

found that the disease which was diagnosed as nephritis seemed to follow two courses. These are known as Type I and Type II nephritis. The nature of these entities are set forth in Table II:

Table II

	Type I Abrupt Onset	Type II Insidious Onset
General Symptoms	+	—
Hematuria	+	— or slight
Previous infection	+ 84%	Less than 5%
Edema	Short duration	Persistent
Age Incidence	60% less than 20	All decades 50% between 10 & 30 30% over 40
Recovery	Greater than 80%	Less than 5%

(after Ellis)

Professor Ellis included under Type II those cases which are known as lipoid nephrosis. He found in those cases of liquid nephrosis which came to post mortem that the histological picture found in the kidneys was the same as that found in Type II nephritis.

The problem of whether the nephrotic syndrome (Type II) and acute glomerulonephritis (Type I) have a different etiology has never been settled.

There seems to be no doubt that a streptococcal infection always precedes the onset of acute glomerulonephritis (Type I). This is further substantiated by the high antistreptolysin titre found in patients suffering from this disorder. The disease is felt to be the result of an antigen antibody reaction occurring in the kidneys of a person who has a sensitivity to streptococcal toxins. Animal experiments have lent support to this conception of acute glomerulonephritis.

It is impossible at the present time to implicate a previous infection as the precipitating factor in the production of the nephrotic syndrome. There is seldom a history of an infection preceding the nephrotic syndrome, and the antistreptolysin titre is extremely low. However, the possibility of subclinical infections cannot be excluded, and it is known that there is great loss of gamma globulin, and hence of antistreptolysin, in the urine of the nephrotic.

Even though the histological and clinical pictures of these two syndromes may appear different, it may well be that one etiological agent may produce lesions which differ in appearance.

Pathology of the Nephrotic Syndrome

The pathology of the nephrotic syndrome depends much upon the stage at which the kidneys are seen. In the early stages the kidneys are normal sized or slightly enlarged. The cut surface shows a marked cortico-medullary differentiation, and there are yellow areas of fatty change scattered diffusely over the surface. The cortex has a greasy feel. In the early stages the most marked microscopic changes are seen in the tubules. These consist of lipoid deposition in the cells of the proximal tubules. However, although the tubular changes are most easily recognized, the changes in the glomeruli are the most important in the pathogenesis of the nephrotic syndrome.

The early glomerular changes in the nephrotic syndrome are of two main types.[2]

1. Membranous glomerulonephritis—This lesion consists of an acidophilic thickening of the walls of the glomerular capillaries. As the disease becomes more chronic, the lesions become more acidophilic, granular, vacuolated, and more porous looking. This type of lesion is responsible for lipid nephrosis, and the nephrotic syndrome seen with cortisone therapy, x-radiation, nitrogen mustard, TEM, 6-MP, penicillin, gold salts, tridione, eclampsia, malaria, febrile albuminuria, and in lupus erythematosus.

2. Lobular Glomerulonephritis—This glomerular lesion consists of 4-5 acidophilic masses surrounded by dilated capillaries. Lobular glomerulonephritis is responsible for the nephrotic syndrome which is complicated by hypertension, renal insufficiency, some degree of hematuria, and pyuria.

If the disease progresses, both the membranous and lobular forms of glomerular change undergo a progressive sclerosing reaction, with the obliteration of the glomerular capillaries, tubular atrophy, interstitial fibrosis, arteriolo and arteriosclerosis, and finally reduction in renal size with the development of granular contracted kidneys.

As this sclerosing lesion of the kidney progresses, there is at the same time a reduction in the proteinuria, and the development of a polyuria with a low urinary specific gravity, a loss of edema, the development of hypertension, the lowering of the blood levels of alpha and beta globulin, and the elevation of gamma globulin (vide infra), along with a feeling of improvement by the patient until renal decompensation results in death. The process of sclerosing is extremely variable—40% of cases are dead within 5 years, but some cases take up to a dozen years for this process to become evident.

Pathophysiology of the Nephrotic Syndrome

Proteinuria: The cause of proteinuria is the result of increased glomerular capillary permeability.[3] It is felt by most that this increase in permeability is the result of the glomerular pathology. The proteinuria results in the loss of albumin, (which accounts for 90% of the urinary protein), gamma globulin, and Protein Bound Iodine. These all, in turn, produce hypoproteinemia.

Hypoproteinemia: This has been shown to be due to the urinary loss of protein alone. There is increased liver production of plasma proteins; and muscular wasting, which occurs in the nephrotic syndrome, must contribute somewhat to the level of plasma proteins.

Edema: In 1896, Sterling showed that the factors controlling the transfer of fluid across the capillary wall are the hydrostatic pressure of the blood in the capillary tending to force fluid out; the colloid osmotic pressure of the plasma proteins tending to hold the fluid in; the integrity of the capillary wall, which prevents the loss of plasma proteins to any great extent, thus conserving the colloid osmotic pressure of the plasma; and the pressure of the interstitial space. The mechanism of edema production in the nephrotic syndrome has been investigated by J. R. Squire.[4]

He has shown that the reduced levels of plasma proteins result in a marked decrease in the colloid osmotic pressure of the plasma. In his experiments, Professor Squire has shown that the relationship between colloid osmotic pressure and the concentration of plasma proteins is not a graphic straight line, but rather a curved one, so that in normal serum small changes in protein concentrations result in relatively large changes in colloid osmotic pressure. Thus, in a normal subject, loss of fluid from the capillaries would cause an increase in plasma protein concentration and hence in colloid osmotic pressure of the plasma, preventing further loss of fluid.

In the nephrotic syndrome, however, this regulatory mechanism is lost because of the extremely low levels of plasma proteins, and large volumes of fluid would be lost before the osmotic pressure of the plasma would become of sufficient magnitude to prevent further loss. Further, Squire has shown that the gradient relating plasma protein to colloid osmotic pressure is flattened in the nephrotic syndrome. Thus a much larger fluid shift than normal can occur before there is a sufficient rise in osmotic pressure to oppose the fluid loss.

Another factor concerned in the transfer of fluid across the capillary wall is the pressure in the interstitial space. The interstitial space is occupied by the ground-substance, which is a colloid gel. This gel has an affinity for water and tends to draw water out of the capillaries and to resist its re-absorption. The swelling pressure of the colloid gel is reduced to zero if the gel's affinity for water is satisfied completely. The arrival of more fluid from the capillaries would then result in a collection of free water lying in the interstitial space and the appearance of edema.

The possibility of the edema of the nephrotic syndrome being the result of generalized increased capillary permeability has been ruled out by the observation that samples of edema and ascitic fluid show low protein values, and negligible colloid osmotic pressures. This evidence may be regarded as excluding gross capillary permeability to colloid as the cause of edema.

Although most observers feel that the hypoalbuminemia is the most significant factor in the production of edema, there are some facets of the disease that cannot be explained on this basis alone. It has been found by several workers that infusion agents such as salt-free albumin or dextran, result in diuresis following a rise in the osmotic pressure of the plasma. However, it has also been shown that a spontaneous diuresis may occur without any measurable increase in the plasma protein concentration.[5]

Squire has found that the plasma volume in the nephrotic syndrome is reduced, and he points out that any increase in circulating albumin would probably cause an increase in the plasma volume rather than an increased albumin concentration; the mechanism being as follows:

1. infusion of albumin into nephrotic vascular system
2. elevation plasma albumin level resulting in
3. increased colloid osmotic pressure
4. flow of fluid from interstitial space into the vascular space producing in increased plasma volume
5. and lowering of the colloid osmotic pressure of the plasma as the result of lowered albumin concentration.

The mechanism whereby spontaneous diuresis occurs without an increase in plasma protein concentration has yet to be elucidated. It has been shown that there is a sodium retention in the nephrotic patient, and that when a diuresis occurs there is also an increase in sodium excretion. The cause of this sodium retention appears to be related to the production of a sodium retaining corticoid, which has 15 - 20 times the sodium retaining power of desoxycortisone.[6] This hormone has been isolated in the urine of nephrotic children. The production of antidiuretic hormone in the nephrotic syndrome has been shown to be elevated. The significance and mechanism, whereby posterior pituitary is stimulated, has not been clearly elucidated. Some[7] postulate the existence of volume receptors which are stimulated by the fall in plasma volume in the nephrotic syndrome. These receptors sending reflex stimulation to the posterior pituitary and to the adrenal cortex result in the production of ADH and of sodium retaining corticoid.

Hyperlipemia: The cause and the significance of the hyperlipemia which occurs in the nephrotic syndrome is not understood. There is a rough correlation between the degree of hypoalbuminemia and hyperlipemia. The lipid pattern in nephrosis is altered. Normally, nearly all lipids of the plasma are associated with the alpha-1 and beta-1 globulins. In nephrosis there is marked diminution of the alpha lipoproteins and an increase in the beta lipoproteins.[8] This is shown in Table III.

Table III

	Normal	Nephrotic
Alpha-lipoproteins	29% total cholesterol	5% total cholesterol
Beta-lipoproteins	64% total cholesterol	92% total cholesterol

Clinical Manifestations of the Nephrotic Syndrome in Children

Age Incidence: In children, the disease manifests itself during the second or third year of life in one-half the cases, and before the fifth year in two-thirds of cases.[8] Professor Ellis, in reviewing the cases at the London Hospital found that in Type II nephritis, 50% of cases occurred in a scattered distribution throughout the whole age period. He found that one-third of his patients were over the age of 40.[1]

Sex Incidence: There seems to be no relationship to sex, the nephrotic syndrome occurring equally in both sexes.[1]

Family History: There seems to be no definite familial incidence of the nephrotic syndrome. However, Barnett[8] found a family history of allergy in 28% of cases.

Edema: Although edema may be present constantly after the onset of the disease, it is more characteristic that the edema vary with periods in which the edema is completely absent. The onset of remission of edema often follows an acute infection. However, they do occur more commonly in a spontaneous fashion. The exacerbations or remissions of the edema may last weeks or months; although the duration of the disease may be as short as several weeks, it is usually measured in terms of months or years.[8]

Gastro - Intestinal Disturbances: Diarrhoea is common during periods of massive edema, and has been attributed to edema of the intestinal mucosa.[8]

Intercurrent Infections: Children afflicted with the nephrotic syndrome are prone to the development of secondary infections. It has been shown that there is a loss of gamma globulin in the urine of nephrotics. In this manner these children are, in essence, converted to a condition not unlike agammaglobulinemia. These children, for this reason, require an extremely high dose of gamma globulin to protect them from measles or infectious hepatitis.[8] It is claimed that any reduction in the mortality from nephrosis since 1938 has been the result of the introduction of the sulfonamides and penicillin.

Physical Examination: Most of the characteristic physical abnormalities are related to edema. The veins on the anterior abdominal wall are frequently dilated in children with persistent ascites. Rectal prolapse is not uncommon, as is the development of an umbilical hernia. Hepatomegaly is a frequent physical finding; the size of the liver decreases during recovery.[8]

Laboratory Findings

Urine: In the acute stage of the disease, the volume of the urine varies inversely with the development of edema. Proteinuria is marked: 90% of the urinary protein is albumin, the remainder is composed of alpha, beta, and gamma globulin; there is no fibrinogen. There is a diminished threshold for glucose, and alimentary glycosuria may occur. The urinary sediment shows doubly refractile lipoid bodies when viewed through polarized. light. This latter finding is said to exist in all conditions in which there is a lipoid degeneration of the tubules. Addis counts show 200 - 800 thousand red blood cells in twelve hours, which is much less than is seen in acute glomerulonephritis, (Type I).[9]

Blood: There is marked decrease in the total plasma proteins. The protein profile is as follows:

Albumin	decreased
Alpha globulin	increased
Beta globulin	increased
Gamma globulin	decreased
Fibrinogen	normal or increased

The change in plasma proteins results in an increased erythrocyte sedimentation rate.

The serum lipids are markedly increased in the nephrotic syndrome. The serum cholesterol level may range from 300 - 1800 mgm%.[10]

Despite the extreme pallor which is seen in nephritic children, anemia is an uncommon finding.

Skeletal Decalcification: This is said to be the result of increased loss of calcium proteinate in the urine and the stools.[8]

B. M. R. This has been shown to be lowered in the nephrotic syndrome. There is a loss of protein bound iodine in the urine along with the albumin fraction. However, the I-131 pick-up in nephrotics has been shown to be normal or increased. The cause of the lowered B.M.R. has not been explained, but some feel that it is related to the insulating effects of the massive edema[8]

Prognosis of the Nephrotic Syndrome

There seems to be some confusion in the literature regarding the prognosis of the nephrotic syndrome. It would appear that the prognosis of nephrosis as seen in children differs greatly from Type II nephritis as described by Ellis. Professor Ellis found that in those cases which followed the pattern of Type II nephritis, the mortality was greater than 95%.[1] However, he pointed out that most of the mortality of these cases was the result of infectious processes. Thus, if one considers that the cases which Ellis reviewed were those occurring over a twenty-year period prior to 1942 (for the most part in the pre-antibiotic era) it is not surprising that his cases had a higher mortality than more recent pediatric series.

The prognosis given from various pediatric series varies somewhat, and this variation seems to be the result of the period during which the cases were reviewed. Schwarz et al (II) writing in 1935, in the pre-antibiotic era, found that about half of the children died as a result of nephrosis, about 25% seem to recover completely, and the remaining 25% either gave no clinical symptoms of nephrosis but showed albuminuria, or were unimproved. The authors of this latter series conclude their article with the following statement . . . "recovery from lipoid nephrosis depends upon the ability of the patient either to escape or to recover from a severe secondary infection".

A more recent pediatric series by Barness et al[12], published in 1950, shows a marked improvement in the prognosis of the nephrotic syndrome; about one half of the cases recovered completely without residual disease, while a small number showed persistent albuminuria and/or hypertension.

Attempts have been made to determine whether any of the renal function tests might be of use to determine the ultimate prognosis of an individual case of nephrosis. The results of these experiments to date have been unsuccesssful. It has been found that the glomerular filtration rate is frequently, but not uniformly, reduced in nephrotics who have (or will) develop evidence of renal insufficiency. A rapid reduction in the glomerular filtration rate is often the first evidence of a rapidly fatal course. Occasional fluctuations in both directions are seen in nephrotics.

The filtration fraction (glomerular filtration rate/plasma flow) is reduced in most cases of glomerulonephritis. In patients who do not go on to renal insufficiency, the glomerular filtration rate, the filtration fraction, and the TmPAH remain normal throughout, except when the disease is complicated by infection, when they are reduced.[13]

Treatment of the Nephrotic Syndrome

Since the etiological agents of the nephrotic syndrome are not all known, no known therapeutic agent or method of prophylaxis has yet been discovered.

The treatment of this condition, for the most part, is designed to reduce edema. The following are the methods currently in vogue:

1. Sodium Restriction. This may be accomplished by restricting the dietary sodium. The use of ion exchange resins may produce a greater degree of sodium restriction. It seems to this writer, however, that the unpalatability of these compounds preclude their use in pediatric practice.

2. Correction of Protein Starvation. If the renal function of the patient is not impaired, then a high protein diet may be given without fear of producing uremia. Following the administration of a high protein diet, the BUN may rise. However, if the renal function is not impaired (as evidenced by a normal ability to concentrate the urine) then no deleterious effects will result. If a high proportion of carbohydrate and a fat are given along with an adequate protein supply, then protein catabolism will be diminished.[9]

3. Oncotic Agents. Plasma, salt-free albumin, dextran, etc., result in a transient elevation of the plasma osmotic pressure, and thus in a transient amelioration of the edema of nephrosis. The use of oncotic agents may be most effective where, following their administration, sodium restriction alone may be enough to control edema.[9]

4. ACTH and Cortisone. To date these agents seem to be the most logical therapeutic approach to the lesions of the nephrotic syndrome. A diuresis is said to occur in 80% of children given a single course of ACTH.[13] Following such an induced diuresis, there may be almost immediate reaccumulation of the edema, a variable period of remission with later exacerbation, or occasionally complete healing.

The following changes in the pathophysiology of the nephrotic syndrome have been observed following the administration of hormone therapy:[8]

(1) Decreased proteinuria during and following the administration of ACTH.

(2) Increased GFR occurring at the time of diuresis in children whose rates were reduced before treatment.

(3) A decrease in serum lipids.

(4) A fall in the sodium retaining corticoids at the time of diuresis.

(5) Reversion to normal exchange of sodium and potassium in the renal tubules.

(6) A rise in serum complement.

It has been shown by Lauson et al[14] that the administration of ACTH results in a restoration to normal of the increased glomerular permeability seen in the nephrotic syndrome. It is possible that the above-listed effects of hormone therapy are all the result of this restoration.

5. Mechanical Removal of Fluid. If the collection of fluid interferes with respirations from either abdominal fluid or pleural affusions, then paracentesis is indicated.

6. Diuretics. These may be used in an attempt to control edema. Fishberg[4] states that if the patient has been previously prepared with ammonium chloride, and then gets no response to the diuretic, then frequently further use of the diuretic also fails to induce a diuresis.

7. Prevention of Intercurrent Infections. Patients suffering from the nephrotic syndrome have a loss of gamma globulin in their urine, and a resulting diminution of plasma globulin, thus making them more susceptible to infection. It is for this reason

that these children should be guarded from contact with infections, and when they do contract an infection, the latter should be treated vigorously. Some authorities advise the use of continuous prophylactic antibiotics.

8. Infection with Measles. Remission of the nephrotic syndrome has been shown to follow an attack of the measles. Whether this is a non-specific stress resulting in increased production of endogenous corticoids has not been proven.

9. Bed Rest. This seems to be indicated only if the edema is of such great magnitude as to prevent ambulation, or when a secondary infection exists.[8]

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Medicine

Some Important Aspects of Medicine in 1955

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There are few subjects in Medicine of which it can be said that no advance is made from year to year, but the spotlight of medical interest tends to shift and each year certain subjects tend to take precedence over others. General Medicine has become such a large field and its literature and that of its sub-specialties has assumed such vast proportions, that a brief general review is manifestly impossible. Any selection of subjects from the whole must therefore be an incomplete and arbitrary one, and to some extent reflect the interests of the writers, but it is felt that the subjects selected for this review are of current interest and importance in the Medicine of 1955.

Staphylococcal Infections

Staphylococci have always been one of the most ubiquitous of pathogenic organisms afflicting man and give rise to a wide variety of clinical conditions varying in severity from a minor furuncle to fatal blood stream infections. They may give rise to acute fulminating infections whose course from start to fatal termination is measured in hours or to extraordinarily quiescent and chronic lesions of chronic osteomyelitis. They produce both intracellular toxins with local tissue effects and exotoxins some of which, e.g. the enterotoxin are amongst the most powerful toxins known. Prior to the introduction of Chemotherapy with Sulfonamides in 1937, the mortality rate from blood stream invasion was as high as 80%, and the morbidity from such conditions as chronic osteomyelitis was very high. The Sulfonamides, notably Sulfathiazol, had only a limited antibacterial effect on the staphylococcus and while reducing mortality to a minor degree had little effect on the overall picture of staphylococcic infections.

When Penicillin was first used in the treatment of bacterial infections it was evident that it was a powerful antistaphylococcic agent, and the clinical response of severe staphylococcic infections was dramatic. While occasional strains of staphylococcus were apparently completely resistant to Penicillin, these were the exception and the great majority were highly sensitive. The mortality rate for generalized staphylococcal infections dropped precipitously from its former high level to about 30%, and in the space of a few years the incidence of certain types of infection, notably osteomyelitis, dropped. A new era had apparently dawned. Throughout the World, and probably more especially on this continent, Penicillin received widespread use and as time progressed increasing numbers of Penicillin resistant strains made their appearance, until by 1951 Spink reported 50% of the strains of staphylococcus resistant to Penicillin. A parallel sequence has followed the introduction of each new antibiotic, including Streptomycin, and the Tetracyclines, but fortunately not to the same extent with Erytromycin, Chloramphenicol, or the potentially toxic antibiotics Neomycin and Bacitracin, probably because of their more limited application to the treatment of infections. In the Winnipeg General Hospital, Doctor J. C. Wilt reports that 80% of strains of staphylococci are now resistant to Penicillin, and that most Penicillin resistant strains are now resistant to Tetracyclines. About 40% of strains are resistant to Chloramphenicol and 20% to Erythromycin. Expressed somewhat differently, in any

staphylococcal infection in which the sensitivity is unknown, the odds are 4 to 1 against Penicillin being effective, and almost as great against the Tetracyclines. Conversely, the odds at present are 4 to 1 that Erythromycin will be effective and 3 to 2 that Chloramphenicol will be effective.

Two forms of antibiotic resistance occur: The first, and by far the most uncommon, is the gradual development of resistance — the organisms being capable of surviving in the presence of Penicillin but not producing penicillinase. When Penicillin is removed from the environment the resistance is lost. The second and by far the more common and important type is one characterized by the sudden development of resistant forms which elaborate penicillinase and which retain this characteristic through succeeding generations. It is believed that these strains develop as mutations, and when sensitive strains are wiped out the resistant strains are permitted to thrive. In a given community there is a tendency for one type or strain to predominate, and there is evidence that in time the predominant strain tends to die out and be replaced by another resistant or even sensitive strain. In general, it is probably true that the incidence of resistant strains in a population is indicative of the degree to which that population has been or is being exposed to antibiotics. It would appear that hospitals, where antibiotics are extensively used, constitute the focus from which resistant strains are disseminated throughout the community both by patients and staff.

Troublesome and serious forms of staphylococcic infection are becoming a problem in most large hospitals today. Not only do they manifest themselves as various forms of Pyoderma but also as wound infections, as breast abscesses, as staphylococcic pneumonias and as staphylococcic septicemias which all too frequently terminates as a fatal endocarditis, or staphylococcic enterocolitis complicating therapy especially with the Tetracyclines. As recently reported by deVries and Pritchard, the staphylococcus is the predominant organism discovered at autopsy and is presumably the cause of death in many chronic diseases, replacing other pathogenic cocci in this respect.

There can be no doubt that staphylococcic infections constitute a serious problem and one that will probably increase in magnitude. How can it be controlled? Firstly, all the accumulated knowledge of asepsis and antisepsis must be applied with meticulous care in hospital practice. Secondly, the indiscriminate use of antibiotics is to be discouraged and, finally, every staphylococcic infection, particularly in an ill or debilitated patient, must be considered as potentially serious. The organism must be identified and the infection vigorously and promptly treated, preferably by the combination of antibiotics thought most likely to be effective from previous experience, employed in high dosage and for a sufficient period of time to assure eradication, and such therapy combined with proper surgical management of any localized infection.

Neurological Changes of Acute Hepatic Insufficiency: Hepatic Coma

From time immemorial it has been recognized that patients with severe liver disease may, and do exhibit nervous and mental changes which may progress to a state of profound coma and when such occurs, death is the usual result. Such is, however, not always the case, and certain patients recover. In recent years considerable light has been thrown on this subject, and, while the exact mechanism of the neurological disorder has yet to be established, it has been established, beyond doubt, that it does occur in varying degrees, and that in certain instances it is a reversible process.

The syndrome is, usually, ushered in with mental changes simulating other organic dementias. Confusion and disorientation, mania and bizarre behaviour in varying combinations occur, and gradually progress to clouded consciousness, stupor and, finally, deep coma. Accompanying the mental changes are certain objective neurological changes; the irregular flapping tremor, dysarthria, ataxia, increased muscle tone and reflexes, and only in the terminal stages do the plantar reflexes become extensor. Fetor hepaticus is usually present and an important objective sign. Fairly constant, though not specific electroencephalographic changes have been described and histopathological changes in the brain may be demonstrated. It is noteworthy, however, that when recovery does occur, it is apparently complete and without signs of permanent damage.

This sequence of events can be observed under two main sets of circumstances. Firstly, with acute diffuse hepatic necrosis, such as viral hepatitis or chemical necrosis of the liver, and, secondly, when there is chronic liver disease associated with portal hypertension of sufficient duration and degree to have given rise to a high degree of direct portal systemic shunt.

The most common causes of hepatic coma are acute hepatic necrosis accompanying viral hepatitis, and portal cirrhosis with portal hypertension in which there has been decompensation of liver function due to acute hemorrhage, infection, trauma, surgery, acute alcoholic or drug intoxication. Recently, Sherlock and her associates have described chronic intermittent hepatic coma and instances of chronic hepatic psychosis, which they have termed Chronic Portal Systemic Encephalopathy.

While the exact pathogenesis of this state has not been definitely established, some facts seem to have been definitely established. It was first

observed by Pavlov that dogs with an Eck fistula, when fed on meat, developed a neurological disorder culminating in coma, which was reversible. Studies suggested that this was related to the level of blood ammonia or some other nitrogenous substances which bypassed the liver and produced the neurological change. Analogous conditions in man, indistinguishable from hepatic coma have been observed when cirrhotic patients were fed, Ammonium Exchange Resins, Ammonium Chloride or diets high in protein. The exact nature of the nitrogenous substance or substances has not been established, but the evidence indicates that hepatic coma and its prodromata occur when these are absorbed from the gut and cannot be withdrawn from the portal circulation, whether it be because of direct passage through a necrotic liver or through a bypass which is associated with a lesser but severe degree of liver impairment. Further confirmation of this exists in the observation that some patients develop hepatic coma after the establishment of a portocaval anastomosis.

These considerations have offered real and practical help in the treatment of liver diseases, and experience has shown that, when the neurological manifestations appear, they may, in some instances at least, be reversible, particularly in those instances in which they have been precipitated by an acute reduction of liver function complicating cirrhosis. Of prime importance is the attempt to minimize nitrogenous absorption from the gut by feeding a protein free diet, (including lipotropic substances) and providing calories largely, if not entirely, by carbohydrate, orally or parenterally. Attempts to stop severe gastrointestinal bleeding are equally important, as it is a well known source of nitrogen when present in the gut. Absorption of nitrogenous substances of bacterial origin are minimized by "gut sterilization" with a broad spectrum antibiotic, and by initial purgation. When recovery occurs, dietary protein may be introduced. In recent years the importance of a diet rich in calories and protein has been emphasized in the treatment of both acute and chronic liver disease. While the relationship of dietary protein and nitrogenous substances to hepatic coma seems well established, it does not mean that protein restriction should be applied to all cases of liver disease, but rather that it be restricted only in patients on the critical border of acute liver failure, and that patients with cirrhosis or severe viral hepatitis should be carefully watched for the prodromal symptoms, and protein restricted when they appear. There is no evidence that protein or allied substances create the liver damage, but rather that, when liver damage passes a critical stage for a variety of reasons, they give rise to a neurological disorder which may hasten death. There are many other aspects of liver failure still to be elucidated.

Adrenal Insufficiency and Adrenal Steroid Therapy

During 1955, more patients received long courses of Cortisone or its Δ_1 analogue Prednisone for the control of various chronic diseases than ever before. Because it has little or no salt retaining effect, Prednisone has become especially popular, although, apart from salt retention, the side effects of either steroid are very similar. High dosage, above 125 milligrams of Cortisone or 25 milligrams of Prednisone, commonly cause steroid diabetes, metabolic alkalosis, osteoporosis and may precipitate peptic ulceration; however, the purpose of this review is not to stress the complications of administration, but rather the problems that may arise on discontinuing treatment.

Abrupt withdrawal of adrenal steroid therapy may result in an occasional case of acute adrenal insufficiency manifested by apathy progressing to asthenia, nausea, vomiting, peripheral circulatory collapse, fever and death. On rapid withdrawal most patients show mild evidence of adrenal insufficiency, such as listlessness, anorexia and muscle cramps, which disappear in seven to ten days. The cause of such symptoms is undoubtedly delayed reactivation of the adrenal cortex, which has been suppressed by the steroid therapy, and there is good evidence that normal edrenal cortical function may not be attained for several months. Such being the case, added stresses, such as reactivation of the Primary Disease, Intercurrent Infection, Accidental or Surgical Trauma, may precipitate adrenal insufficiency, even though therapy was stopped several months prior to the stressful situation.

As these symptoms and signs may mimic other constitutional disorders, the diagnosis can be easily missed unless the possibility of adrenal insufficiency has been considered. There is no rapid laboratory procedure which will positively confirm the diagnosis, and if any doubt arises as to the cause of vomiting, shock or fever in a patient recently treated with Cortisone or Prednisone, an immediate therapeutic trial of intravenous Hydrocortisone is indicated. This may be administered in an intravenous drip, as fluids are usually required, and, should the condition be due to adrenal insufficiency, improvement will be evident within two hours. No harm will result from the administration of such a dose of hormone, provided saline is not used indiscriminately. The danger of adrenal insufficiency is of particular importance in patients undergoing surgery. Blood pressure may drop precipitously with induction of anaesthesia and will not rise with blood or nor-epinephrine but will rise with intravenous Hydrocortisone which should be available for immediate use.

Patients who have received or who are receiving steroid therapy should be thought of as patients with Addison's Disease controlled on DCA alone or in combination with small doses of Cortisone in

whom a stressful situation may precipitate acute adrenal insufficiency. In the event of acute illness, trauma or emergency surgery they should be fortified with augmented doses of the appropriate steroid, if necessary intravenously.

Hemophilia and Christmas Disease

Within the past five years the mechanism of blood clotting has been intensively investigated, and this new burst of enthusiastic research has brought many new facts to light. Among the most interesting of these has been the attempt to define the coagulation defect in hemophilia. In the course of these investigations it was found that "hemophiliacs" could be divided into two groups. The smaller group, comprising about 10% of the total, differed from the others in that they lacked a clotting factor which was present in normal concentrations in the blood of the remainder. This factor has been designated as Christmas factor, and the lack of this evidence produces a bleeding disorder now referred to as Christmas Disease. True hemophiliacs, however, were found to be deficient in anti-hemophilic globulin which is present in normal amounts in the other group (Christmas Disease). Thus the blood or plasma of the two groups is mutually corrective.

Hemophilia is a hemorrhagic disease due to a deficiency of anti-hemophilic globulin (AHG). AHG is an important link in the chain of thromboplastin formation and in its absence the formation of this substance takes place slowly resulting in a prolonged initial phase of coagulation. The other factors that are important in the generation of thromboplastin include a platelet factor, Christmas factor, and the accelerator factors, Factor V and Factor VII. A deficiency of Christmas factor produces Christmas disease, which cannot be distinguished from hemophilia clinically.

AHG is a labile protein which is found only in fresh plasma and which disappears rapidly from blood or plasma stored at refrigerator temperature. Christmas factor on the other hand is a stable protein which is found in both plasma and serum and can be stored for long periods at 4°C. That is, Christmas factor is present in high concentration in bank blood, while this is a relatively poor source of AHG.

Both hemophilia and Christmas Disease are inherited as sex linked recessives occurring almost exclusively in males. Bleeding usually follows trauma and tends to be severe. Hemarthrosis, subcutaneous and intramuscular hematomas following minor trauma are common and severe prolonged bleeding accompanies minor surgical procedures, dental extractions, etc. The laboratory tests often show a prolonged clotting time in the presence of a normal bleeding time and a normal prothrombin time. This is an indication that the defect is in the initial stage of clotting — in the formation of thromboplastin. A prothrombin consumption test will show little prothrombin consumed as the blood clots — so that there is almost the same concentration of prothrombin in the serum as in the plasma. Normally, almost all of the prothrombin disappears in the process of clotting. Thus far we have not distinguished between the two deficiencies. The specific deficiency may be identified by the Thromboplastin Generation Test which measures the rate of thromboplastin formation from mixtures of platelets, AHG and Christmas Factor, prepared from normals and from the patient. That the differential diagnosis is of some import can be seen from the nature of the two clotting factors. In Christmas Disease transfusion of serum, bank blood or plasma will repair the defect, as these are high in Christmas Factor though poor in AHG. In true hemophilia the transfusion should be of fresh blood, fresh plasma, or fresh frozen plasma which contain both AHG and Christmas Factor.

To arrest bleeding, local measures when applicable include firm pressure, topical thrombin, thromboplastin, or gelfoam. However, as the clot is often of poor quality due to the absence of AHG or Christmas Factor replacement of these factors as outlined above is usually indicated.

Clinical Pathology

Clinical Pathology — 1955

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As factual knowledge is amassed at the dizzy speed which is its present tempo, the boundaries that formerly demarcated one branch of knowledge from another become hazy and disappear. Clinical pathology might be defined as that branch of medicine which applies laboratory procedures to the diagnosis and management of Man's diseases. Even this definition, however, leaves much to be desired because such laboratory manipulations as ventilatory studies, cardiac catheterisations, and electrocardiography are linked more with clinical physiology than with clinical pathology. Similarly intertwining tentacles with clinical investigation, pharmacology, pathological anatomy and so forth are apparent. Bodansky expresses this feeling in his "Clinical Applications of Biochemistry".[1]

"The past 25 years have seen not only a vast acceleration in the application of biochemistry to medicine, but also a marked change in the manner of this application. During the years 1915 to 1930 considerable advances took place in the development of quantitative semimicro or micro methods for the determination of blood, urinary and fecal biochemical components. During this period the accumulation of data concerning the alteration of these components in various diseases helped build a stock of information that was of aid in the diagnosis and management of these diseases and, to some extent also, in understanding of their underlying mechanisms. The development and perfection of such methods and the accumulation of such data have continued, but a new orientation has appeared, namely, the searching out of the basic biochemical lesions in disease, very often on a cellular, enzymatic or even molecular basis."

No world-shaking discovery has been made in this field in 1955, but general advances have been made on all fronts.

Hematology

Hemoglobinometry. The accuracy of laboratory assays has been a great concern, and this has applied to hemoglobin estimations particularly. Samples submitted to a variety of laboratories would indicate that there is too large a number of laboratories that fail in accuracy of such assays. In order to overcome this deficiency it has been recommended that photoelectric methods of determination using cyanmethemoglobin be adopted, and that carefully prepared standards of known strength be made available for periodic check of such instruments. The danger of poisoning from the reagent, which contains cyanide, has been abolished by the use of a reagent which would require a liter to be drunk before lethal dosage would be ingested; unlikely in even the most careless of technicians. It is anticipated that this recommendation will be rather uniformly adopted within the near future.[2, 3, 4, 5, 6]

The subject of abnormal hemoglobins has occupied much space during this year, and has been adequately reviewed.[7] The practical significance of this work is obvious in those parts of the world where negro and Mediterranean populations are present. This work, which was initiated by the Nobel prize-winner, Pauling, is medicine at the molecular level. In addition to the normal adult hemoglobin A, and the fetal hemoglobin F, which appears in adults under abnormal circumstances, hemoglobins C, D, E, G, H, and S have been described. The determination of these types requires chromatography or electrophoresis; methods that are still not widely used in the routine laboratory.

The hemolytic anemias continue to merit much attention. Methods for determination of absorbed agglutinins on the red cells continue to appear and to the well known Coomb's test, and the less well known trypsinized red cell test, there has been added the papain treated red cell test[8, 9, 10]. In a parallel fashion interest continues in agglutination phenomenon to explain cases of leukopenia and thrombocytopenia. Work continues on the establishment of specific blood groups in white cells and platelets, which fortunately appear to be, by and large, the same as for red blood cells.

Increased use of tagged red cells has led to the realization that increased red cell destruction plays a role in many secondary anemias. Wasserman et al have divided these into symptomatic and hemopathic hemolytic anemias, and have reviewed the laboratory manifestations of these[11]. Ham reviews the subject of hemoglobinuria, and the appropriate tests to delineate underlying causes[12].

The branch of clinical pathology dealing with immunological mechanisms that are instrumental in producing blood diseases is now called "immunohematology" and is reviewed[13, 14].

An important advance in the understanding of congenital spherocytic hemolytic anemia has been made[15] where it has been shown that there is a defect in the ability of the red cell to adequately metabolise glucose, and this defect can be overcome by adding adenine to the medium. In addition to leading to a better understanding of this disease and eventually elucidating the enzyme system at fault, it points the way to a specific laboratory test for this disease.

A large number of reports have, as usual, appeared on the coagulation aspects of blood. Good reviews appeared by Seegers[16], Alexander[17] and

McFarlane[18]. Attention has been directed most particularly to the defects in clotting associated with pregnancy and the puerperium where fibrogenopenias have gained the attention of obstetricians. This subject has been nicely summarized[19].

Further methods and modifications of the "LE" cell test continue to appear until the reviewer feels that there are now more modifications of this test than there are sufferers from the disease.

Biochemical Methods

Fractionation of serum protein into smaller components still intrigues the investigator, and measurements have now, surely, been done on all human diseases. A simple method suitable for routine laboratory use[20] is essentially the method described in this Journal in 1953. In spite of all the work done, little diagnostic value is seen for alpha and beta globulins, except under special circumstances, and the simple salting methods seem to give almost as much information as the more elaborate electrophoresis and paper chromatography. Agammaglobulinemia continues to excite curiosity[21] since its description by Burton in 1952. The observation by Good[22] that those individuals who suffer from congenital agammaglobulinemia show absence of plasma cells histologically is of extreme interest, and may be marked as the most significant advance of the year. If true, this would give strong support to the school that favors the plasma cells as the source of antibody. It would also suggest that the pathway along which plasma cells develop from precursors can be blocked. If this could be blocked at will, it might offer an approach to the therapeutic problem in myeloma; and, possibly, as well to those diseases in which antibody formation becomes harmful to the individual.

A modification of a method, at present used to determine uric acid in serum, has been described[23], which in our experience is a useful technical advance. Zak et al have described a new method for estimation of serum cholesterol[24, 25], which is simple and useful.

Assays of epinephrin and norepinephrin may be of use in the diagnosis of pheochromocytoma, but are not technically easy. The subject is reviewed[26].

New techniques for the assay of 17-ketosteroids continue to appear, and also for corticoids. A simple laboratory procedure for the assay of pituitary gonadotropins in the urine[27] also appear to be useful in the occasional case.

Aldosteronism is one of the latest of clinical syndromes described, and methods for assay of the hormone have appeared[28].

A number of methods for determination of serum calcium using colorimetric procedures and employing a chelating agent and a dye have been reported, but although on paper they appear promising we have not found them as simple or reliable as the standard oxalate method[29].

Various Systems and Organs

The year continues to bring reports of new liver function tests or modifications of existing ones — all attesting to the inadequacy of present tests. A number are, again, of the flocculation variety — one of the most recent is APG (acid precipitable globulin)[30]. We have been rather disillusioned by the various water, alcohol, iodine, cadmium, etc. flocculation tests, and have stopped even trying them, as in our hands they have not proven any better than the old familiar thymol turbidity and flocculation tests, and the gamma globulin estimation.

Reports on the assay of blood[31] and spinal fluid[32] ammonia levels in hepatic coma and precoma are still of interest, although the correlationship is apparently not good enough to be of much clinical utility.

In the field of renal function little new has appeared, however the wider application of renal biopsy is undoubtedly a great advance in the diagnosis and understanding of renal disease[33, 34].

There is now a huge volume of papers on various aspects of the serum in atherosclerosis which indicates the interest in this subject. There seems to be little doubt that abnormal serum lipids are associated in most cases at least, with coronary atherosclerosis. The obvious implications are that the clinician should be able to discover the susceptible individual before myocardial infarction has occurred, although whether or not he can circumvent the anticipated disaster is not known.

Cancer tests continue to appear regularly. Various serum enzymes are the current field of interest[37] and isomerase, lactic acid dehydrogenase, and succinic acid dehydrogenase would appear to be elevated in metastatic carcinoma. However no test has yet been devised that appears any more specific or accurate than the erythrocyte sedimentation rate. Incidentally two reports from the same observers dealt with the persistent unexplained rapid sedimentation rate[35, 36] which is seen particularly in females, very rarely in males, and tends to be associated with the sicca syndrome and with various abnormalities of the serum proteins.

Another serum enzyme, amylase, has been found elevated in 82% of mumps with no evidence of pancreatitis[38], and is suggested as a useful diagnostic test in obscure cases that may be mumps, e.g. encephalitis.

In order to overcome the aesthetic trauma of a stomach tube for gastric analysis, a "tubeless gastric analysis" has been proposed based upon the exchange of quinine for hydrochloric acid in an exchange resin fed to the patient, and its subsequent excretion in the urine[39]. This has been simplified by Segal et al, who use Azure A dye

in an exchange resin and then examine the urine for the color of the dye[40]. Examination of the urine for pepsin has been currently engaging the attention of investigators and this subject is reviewed[41, 42]. The truth of the matter is, however, that if one wishes to be certain as to whether or not achlorhydria is present he still must fall back on the old fashioned tube.

Other topics have been dealt with in the current literature, such as red cell survivals, blood volume determinations, fat absorption studies, pancreatic function tests etc., and the whole field of isotope studies is, of course, very active and is gradually edging into the diagnostic field of clinical pathology.

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Therapeutics

Therapeutic Advances — 1955

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Any review of therapeutic advances must take into account the chronological development of the type of treatment under consideration. Any new treatment goes through an initial phase of enthusiastic approval marked by voluminous literature, a secondary phase of rejection with a small number of critical articles, and a final phase of stabilization as an important measure, or total rejection of its value. Some of the major advances, such as antibiotics and steroids are attaining the third or final phase. Coincident with the great number of drugs being released for general use there is a growing realization of the very real dangers of toxic reactions occurring in humans that cannot be forecast by short term experiments in laboratory animals.

Antibiotics remain the most important field in modern therapy. Unfortunately, widespread and indiscriminate use of antibiotics has resulted in the spread of antibiotic resistant organisms. The staphylococcus has caused the greatest concern by its ability to rapidly mutate into a resistant organism. The use of various antibiotics as an "umbrella" to prevent infection in surgical and medical patients, has resulted in patients, staff, bedding and equipment becoming heavily laden with antibiotic resistant bacteria. This will necessitate a rapid return to segregation of infected patients and the use of antibiotics only when clearly indicated. Studies with the routine use of an antibiotic in an infection, such as measles, to prevent bacterial secondary invaders have shown that the antibiotic does not prevent these infections, but only promotes invaders that are resistant to the bacteria. The widespread use of an antibiotic such as erythromycin which, initially, was potent against the staphylococcus has rendered this antibiotic less valuable in hospital infections. Fortunately, chloramphenicol was shown to have rare but serious toxic reactions that curtailed its use. This fact will undoubtedly prolong its useful life in the treatment of staphylococcal infections, particularly if it is only used when indicated clinically, and its value proved bacteriologically. It is hoped that new antibiotics such as "Cathomycin" that are effective against the staphylococcus will not be used indiscriminately and will be reserved only for the most serious infections. Hospital staffs would be well advised to arrange restrictions on the use of any new antibiotic to delay the appearance of strains resistant to the new antibiotic. Perhaps, it is only just that penicillin has come into its own again, as (a) the drug of choice, in massive quantities, in fulminating staphylococcal infections such as septicemia, even when in-vitro tests would suggest the organism is resistant; (b) the drug of choice in large doses, and in conjunction with streptomycin, in the resistant strains of bacteria in subacute bacterial endocarditis; (c) a useful drug in streptococcal pharyngitis employed in adequate quantities over seven to ten days to lessen the incidence of rheumatic fever and acute nephritis. Fatal anaphylactoid reactions from penicillin, both parenterally and orally, continue to be reported, and it is mandatory to enquire for previous reactions before giving it. Oral peni-

cillin is a useful drug, but serum levels after administration by this route have not been reliable. A new type of penicillin, penicillin V, seems to be superior in its dependability of levels after oral use.

Adrenal steroid therapy is coming of age. This event has been marked by the publication of carefully controlled studies on the use of steroids in early rheumatoid arthritis and acute rheumatic fever as compared to the use of salicylates. This means that steroids, although useful in a few cases, should be used with circumspection in these disorders. A further mark of the maturity of steroid therapy has been the appearance of new steroids, prednisone and prednisolone, which have none of the electrolyte effects of cortisone or hydrocortisone, though retaining their other properties, both for good and evil. Another new steroid is 9-alpha-fluorhydro-cortisone which is effective topically and orally and has marked sodium retaining properties that should make it useful in Addison's disease, though limiting its use in other disorders. Systemic use of steroids are valuable in allergic and hypersensitivity states, lupus erythematosus disseminata, dermatomyositis, nephrosis, sarcoidosis and in palliation of leukemias, lymphomas and metastatic carcinoma of the breast. Topical use of hydrocortisone is effective in many ophthalmological and dermatological diseases, but, even then, it is contra-indicated in herpetic corneal ulcers. Two uncomfortable, but benign disorders, mumps orchitis and severe infectious mononucleosis, can benefit greatly by brief courses of steroid therapy. The major danger of steroid therapy appears to be the suppression of the patient's own adrenal. This makes imperative the administration of extra steroids in times of "stress" of surgery, trauma or illness, if the patient has received steroids any time in the past year. Intravenous hydrocortisone is most useful in times of emergency like these, or in the crises of Addison's disease.

The number of new drugs coming into use forces the physician to be alert to possible toxic reactions. Toxic reactions may appear in a multiplicity of forms, but some of the more important are:

1. Toxic hepatitis, e.g. chlorpromazine ("Largactil"), phenylbutazone, methyl-testosterone.
2. Agranulocytosis, e.g., phenylbutazone, thiouracil.
3. Hemotoxic, e.g., phenylbutazone, thiouracil, chloramphenicol, quinidine, and many others especially with benzene ring combined with N, NH or NH_2 radicals.
4. Rashes, e.g., penicillin, barbiturates and many others.
5. Anaphylactoid, e.g., penicillin.

Inevitably toxic reactions to drugs are going to be an increasing problem, so watch for toxic reactions, particularly in new drugs. Disodium calcium versenate has proved valuable in lead poisoning. A new barbiturate antagonist, methyl ethyl glutarimide is promising in initial reports, though maintenance of adequate pulmonary ventilation is still imperative.

One of the major advances in the therapy of respiratory diseases has been the emphasis on maintenance of adequate pulmonary ventilation. In cases of coma with respiratory depression, tracheotomy and tracheal suction may be life saving. In severe emphysema the pulmonary ventilation may be so inadequate that carbon dioxide is retained and the oxygen is lowered. The addition of bronchial infection and bronchial obstruction may precipitate severe respiratory acidosis with mental confusion and coma. Simple administration of oxygen in such cases may intensify the difficulty. However, mechanically assisted respiration, the use of bronchodilators in an aerosol form, and the administration of antibiotics can bring dramatic relief to these cases.

In the field of blood diseases the more accurate diagnosis of the hemolytic and hemorrhagic disorders has placed treatment of these disorders on a rational basis. In pernicious anemia, Vitamin B_{12} in adequate doses parenterally (30 micrograms twice monthly) is the treatment of choice. Unfortunately certain multivitamin preparations contain folic acid in sufficient amounts, that, if given to patients with undiagnosed pernicious anemia, may cause a crippling neurological relapse, even though the blood may return to normal levels (making the diagnosis even more difficult). Multivitamin compounds containing folic acid should be avoided at all costs. Pharmaceutical firms make such preparations available only because physicians prescribe them. Simple and inexpensive iron preparations such as ferrous sulphate and ferrous glutonate continue to demonstrate their superiority in treatment of iron deficiency anemia over elaborate and expensive "shot gun" mixtures, especially those with folic acid in them. Intramuscular iron-dextran mixtures, or intravenous iron preparations are useful where iron is not tolerated or absorbed. In leukemias and lymphomas the chemotherapeutic agents appear to promise a superiority over radiation in the palliation of these disorders.

The field of surgical therapy of congenital and acquired valvular heart disease is still in the initial phase of enthusiasm. This phase has been prolonged with the use of hypothemia and cross transfusions in extending the range of the surgeon. Likely, at present, all congenital heart disease and valvular heart disease in patients of a reasonable age should be given the advantage of a careful anatomical and physiological diagnosis to see if surgery can aid them, if not now, perhaps in the future. In acute myocardial infarction the use of anticoagulants is an accepted procedure, although

a minority of authors maintain that the mild cases do not require anticoagulants. Long continued use of anticoagulants to prevent further episodes of coronary occlusion in individuals with severe coronary artery disease is being advocated by many. Until further definitive reports are available, the non-committal Scottish verdict of "not proven" must be handed down. An excellent case for a lean body build and a low fat - low cholesterol diet can be made for the prevention of atherosclerosis. However, it is more difficult to establish the worth of such a regime, other than as a reducing diet, as a therapeutic procedure in reversing or slowing the atherosclerotic process. In severe congestive heart failure the administration of "Diamox" or ammonium chloride for 2 or 3 days prior to a mercurial diuretic and followed by intravenous aminophylline may provoke a vigorous diuresis. The role of potassium depletion in severe heart failure and in digitalis intoxication is receiving emphasis and the oral administration of 2 - 3 gms. potassium chloride in patients with good renal function has some virtue. Likely, the oral diuretics are only of value in the mild cases of failure.

Drug treatment of essential hypertension is in the enthusiastic phase, and accurate assessment is not possible. In the author's opinion, the use of pentolinium ("Ansolysen") in conjunction with R. serpentina or its derivatives, is of distinct value in severe hypertension, such as Grades III or IV. Medical management of such a case is time consuming, both for the patient and doctor, and not without danger, and whether results with these drugs will be superior to sympathectomy remains to be seen. Hydralazine ("Apresoline") has a grave disadvantage in its toxic effects — bone marrow depression and a lupus erythematosus-like syndrome that limits its use. The derivatives of R. serpentina have been strongly advocated in the milder stages of hypertension, but evidence is not yet available as to any real effect over a long term, and should be regarded as the "rich man's phenobarb" at present.

Adrenal steroids given intermittently or continuously represent a real advance in the treatment of the nephrotic syndrome in children, even though both measles and malaria produce similar remissions. In acute anuria the value of the conservative treatment of this syndrome is well established. The use of 40% glucose solutions given intravenously through polyethylene catheters into the vena cava is of distinct aid in the management of acute renal failures.

No striking therapeutic advances have been made in gastro-intestinal diseases. The problem of the management of peptic ulceration is as vexing as in past years, and the anti-cholinergic drugs available give temporary relief. In liver diseases the recognition of impending hepatic failure, and the role of increased protein intake in producing hepatic "coma" has been a notable advance. The use of high carbohydrate and extremely low protein diet may tide these patients with advanced liver disease over these episodes. However, when the patient is able to tolerate a high protein, high calorie diet recovery is accelerated, both in chronic liver disease and acute viral hepatitis. Studies performed in Korea and Japan have shown that patients with viral hepatitis can tolerate activity up to bathroom privileges, and that strict bed rest is not necessary after the very acute phase, and that the patients may be returned to full activity rather more rapidly than had been believed.

In Cushing's disease the effect of bilateral adrenalectomy has been most gratifying. Perhaps it is always worthwhile to try the effect of pituitary irradiation in females with Cushing's disease, but it is almost useless in males with this disorder. The delineation of the rare syndrome of "primary aldosteronism" due to adenoma of the adrenal, and its relief by surgical removal has been notable. Prednisone is the drug of choice in the treatment of virilism due to adrenal cortical hyperplasia.

Perhaps one interesting development in neurological disorders is the interest in transient cerebrovascular accidents. It appears that these may be due to abrupt elevations of blood pressure in hypertensive patients, the so-called "hypertensive encephalopathy" and the various potent hypotensive agents may be of value here. In other cases these transient attacks may indicate intermittent insufficiency of the basilar or carotid arterial system and anti-coagulants may be of distinct value. Further progress in the field can be expected.

The author wishes to state that many of these opinions are dogmatic and arbitrary and wishes to reserve the right to change his opinion at a moment's notice.

Ophthalmology

Recent Advances in Ophthalmology

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It is difficult to pick out any strikingly new discoveries which have been made this year, but there are many subjects in which new knowledge has been confirmed and clinical applications better understood. An attempt will be made to assess some of these newer concepts and to present particularly those that may interest general physicians.

a) New Concepts of Disease

Retrolental Fibroplasia

In 1942 Terry first described this condition, and soon after the name was suggested by which it is now known. Terry listed a number of agents which he thought might cause this disease, and pointed the way for the search which led to its cause.

The incidence of this new disease rapidly increased and in a short time it became the commonest cause of blindness in young children. The National Society for the Prevention of Blindness has estimated that it has caused 8,000 children to lose their sight since 1941. Articles upon retrolental fibroplasia have appeared reporting its presence in most of the university centres throughout the world and discussing at length the possible causes of the condition*. The elimination by actual trial of each of these suggested causes one after another reads like a detective thriller.

Excessive administration of oxygen to the premature infant was suspected from the beginning but it was not until 1954 that clinical and experimental studies confirmed this suspicion.

The foetal retinal blood vessels develop from the region of the optic disc. In the seven months foetus they have reached the equator of the eye but they do not arrive at the periphery until just before birth. These immature blood vessels are very sensitive to oxygen excess or lack. The more premature the infant the greater the sensitivity of the retina to oxygen and the greater the risk of retrolental fibroplasia. Fully developed retinal blood vessels are relatively unaffected by changes in the oxygen concentration.

In kittens, mice and rats at full term the retinal blood vessels are still incompletely developed resembling in this respect those of a human seven months foetus. In a series of brilliant animal experiments and controlled clinical observations it has been shown that the administration of excessive quantities of oxygen, particularly concentrations in excess of 45%, lead to constriction of the developing retinal arteries. If the high concentrations are continued the arteries become occluded. On return to a normal concentration of oxygen a relative anoxia of the retina occurs which produces the condition we know as retrolental fibroplasia.

Dilatation and tortuosity of the retinal blood vessels are first seen. Then as the disease progresses new blood vessels appear at the periphery which grow through the internal limiting membrane of the retina into the vitreous. Haemorrhages into the retina and vitreous frequently occur and obscure the fundus details. Retinal detachment begins at the periphery of the retina and may spread to involve the whole retina.

When the disease was first described it was thought that it always led to blindness. Careful observations upon the eyes of large numbers of premature infants have shown that this is not so. It is now realized that many cases do not advance beyond the early stages of dilatation of blood vessels and oedema of the retinal periphery. Later they return to normal.

The treatment of the established condition remains ineffective, but it has been shown that the disease can be almost entirely prevented by restriction of the administration of oxygen to premature infants. Controlled studies have demonstrated that this decreased use of oxygen does not result in an increased mortality. At times the giving of oxygen may be a life-saving measure. In such cases the need for oxygen must be balanced against the risk of retrolental fibroplasia.

The newer incubators which are in every premature nursery are very efficient in providing a high oxygen concentration. This very efficiency is the reason for the appearance of retrolental fibroplasia, particularly in university centres. It is therefore most important that the following practical applications of this new information should be fully understood by all doctors who may have to do with the management of premature infants.

1. Available evidence suggests that the risk of developing the disease is greatest during the first week of life and that it steadily diminishes with every day after birth.

2. Irregular respirations in a premature infant should not be considered an indication for giving oxygen.

3. Cyanosis is the only indication for the administration of oxygen to a premature infant.

4. There is evidence that the longer oxygen is given the greater the risk of developing the disease. Slow weaning from oxygen increases the stay in

*A discussion of this condition and its causes appeared in earlier issues of the Manitoba Medical Review. See Guest, W. C., May, 1954, and Reed, H. and Israels, S., March, 1954.

oxygen and probably increases the danger of retrolental fibroplasia. Oxygen should therefore be stopped as soon as the cyanosis is relieved.

5. Litre-flow is a most unreliable method of measuring supplemental oxygen. Every premature nursery should have an oxygen analyzer.

6. Oxygen concentration should never be allowed to rise above 40%. Clinical studies suggest that a concentration of 40% oxygen is adequate on most occasions for even severe cyanosis and that raising the concentration does not give a better clinical response.

7. The oxygen concentration should be measured and charted every six hours.

In the university centres throughout the world the administration of oxygen to premature infants is now being severely restricted and it appears that retrolental fibroplasia will soon become a rare disease mainly of historical interest. But it will always be remembered as the supreme example of the dangers of excessive medication even when the medicament appears to be so harmless as oxygen.

Pharyngoconjunctival Fever

Increasing interest in the viruses and the study of their cultural characteristics and clinical manifestations has led to the definition of this clinical entity. Several outbreaks of the condition in epidemic form in different areas in the United States of America have aided the study and led to an understanding of its clinical manifestations.

Pharyngoconjunctival fever is infective and has an incubation period of five to ten days with an average of seven. Children are affected in particular but adults may also develop the disease. particularly the mother of affected children. In several instances swimming pools appeared to be the medium of spread and chlorination did not reduce the infectivity of the virus.

Complaints of malaise and headache are common especially in children. Fever up to 104° Fahrenheit may persist for one or two weeks, but this is less frequent in adults. Rhinitis and pharyngitis may be present so that the condition resembles that of a common cold. The cervical lymph glands are usually enlarged. As one would expect there is considerable variation in the clinical manifestations.

One eye is usually affected several days before the other but occasionally the condition remains unilateral throughout its course. In a typical case the palpebral fissure appears narrowed due to swelling of the tissues of the lids and to blepharospasm. Lacrimation is marked but there is no pus. There may be photophobia but this is not a marked feature of the disease.

On everting the lower lid the palpebral conjunctiva is seen to be red and velvety. This appearance is characteristic and is due to proliferation of the lymph follicles of the palpebral conjunctiva. Superficial punctate staining of the cornea is not usually present. The pre-auricular lymph gland is sometimes enlarged and tender.

A smear of a conjunctival sac reveals a mononuclear reaction. Cultures grow Type 3 of the APC or adenoidal-pharyngeal conjunctival group of viruses, but scrapings of the conjunctival epithelium do not show inclusion bodies. This Type 3 APC virus produces a type specific neutralizing antibody in the blood and a slight leucocytosis commonly occurs.

The treatment of this condition is unsatisfactory. No antibiotic appears to be of value in prevention or cure. Fortunately it is a self-limited disease. Most patients recover completely in two weeks and there appear to be no sequelae except an occasional sinus infection.

Thyrotropic or Malignant Exophthalmos

This frightening but fortunately relatively uncommon condition has been recognized for some time. It is a baffling disease, the pathogenesis of which is somewhat obscure. Its relation to thyrotoxicosis is not well understood. Most cases of primary thyrotoxicosis have some degree of exophthalmos and lid retraction and these eye signs subside spontaneously when the thyrotoxicosis is relieved. On the other hand patients with thyrotoxicosis secondary to a toxic adenoma do not show any ocular anomalies.

Moreover, although thyrotropic exophthalmos often follows the treatment of primary thyrotoxicosis by partial thyroidectomy or radioactive iodine, it may occur without previous thyroid disease and in association with a basal metabolic rate which may be low, normal or raised. There is, therefore, no apparent common factor or group of factors causing this condition.

Some years ago it was shown that injections of the thyrotropic hormone into experimental animals caused a condition similar to human malignant exophthalmos. Excessive secretion of this hormone was therefore considered to be its cause, though some workers believe there is a separate exophthalmic factor. Recently, however, it has been shown that the condition can be produced in experimental animals more rapidly and more constantly by giving adrenocortical steroids in addition to thyrotropic hormone.

Thyrotropic exophthalmos is characterized by progressive proptosis, oedema of muscles, an increase in orbital fat, and ocular muscle palsies. Both eyes are usually affected but one may be more severely affected than its fellow. All degrees of severity may be seen from those causing no disability to proptosis so severe that exposure of the cornea involves a risk of corneal ulceration, perforation, and blindness.

The accepted treatment for this condition has not always proved very effective. It is usual to

give sedatives and hormones to depress the anterior pituitary. Thyroxine is the most effective and should be tried first unless the basal metabolic rate is already too high. Other hormones which are less effective are stilboestrol and testosterone. If these fail to prevent further proptosis and exposure keratitis is threatened, the lid margins should be joined together. As a last resort Naffziger's operation of orbital decompression by removing the roof of the orbit may be tried.

Encouraging reports have been published recently on the use of X-ray therapy to the pituitary gland and retro-ocular tissues combined with the administration of thyroxine. In most cases the progress of the disease may be arrested without damage to sight but there is seldom much reduction in the degree of proptosis.

Many of these patients develop ocular muscle palsies which cause disfiguring squints and distressing double vision. When the disease becomes quiescent it is usually possible by appropriate ocular muscle surgery to straighten the eyes and thereby improve the cosmetic appearance and relieve the diplopia.

Perhaps the new experimental findings will lead to more effective hormone therapy.

b) New Diagnostic Procedures

Detection of Early Malignant Melanoma of the Choroid

Every ophthalmologist at times has been faced with the task of deciding whether the patient has an early malignant melanoma of the choroid. This diagnosis may be very difficult when the fundal changes are minimal. If a melanoma is present and it is not removed until late the patient will die from generalized melanomatosis. If the diagnosis is made wrongly then the patient's eye is sacrificed to no purpose. This decision may be even more difficult when the suspected melanoma is in the only seeing eye. Any method therefore that may aid early diagnosis of this condition demands careful assessment.

Recently there have been several interesting studies upon the value of radioactive phosphorus in the diagnosis of intra-ocular melanomata and retinoblastomata. P_{32} is injected into an arm vein. The uptake of this substance in each eye is measured with a Geiger counter and the results compared. It has been found that the eye containing the tumor will take up more P_{32} than the normal eye.

Unfortunately with the Geiger counters used during most of the reported investigations, the results were reliable only for tumors in front of the equator. However, more delicate Geiger counters are being devised, which may be applied to the sclera of the posterior segment. It is possible that this method may prove to be of considerable value in the diagnosis of intra-ocular tumors.

Intra-ocular biopsy is another method which has been suggested for the case in which an intra-ocular tumor is suspected. This is a controversial topic. The objections are that such a procedure might cause severe ocular damage and the manipulation might increase the risk of dissemination of the tumor. But the need for accurate diagnosis is obvious. Sanders has described six cases of suspected intra-ocular tumour in which biopsy assisted in making the diagnosis.

When melanomatosis of the liver is advanced melanogens in the urine may be easily detected by the usual procedures. If it could be shown that chromatography is delicate enough to detect minute quantities of melanin in the urine it may be of some value in the diagnosis of early melanoma of the choroid. This is a method which has not yet been thoroughly investigated.

Glaucoma

Large population surveys in America have indicated that 3.7% of the population over the age of 65 have glaucoma, and that more than half of these people are unaware of its presence. We are living in an aging population and since the incidence of this condition increases with age the numbers of cases of glaucoma are likely to continue to grow. Unfortunately, in far too many patients the vision is seriously impaired before the diagnosis is made.

Recently there has been greater emphasis in ophthalmic literature upon early diagnosis to enable treatment to delay or prevent the progress of the disease. One of the earliest signs of glaucoma is increased intra-ocular tension. A growing number of ophthalmologists include measurement of intra-ocular pressure in their routine examination, particularly in patients over forty years of age. It has even been suggested that general physicians should measure the intra-ocular tension with a tonometer as a routine.

When glaucoma is suspected in an eye, with normal pressure, provocative tests may be used to induce a rise in tension above normal levels, so that a definite diagnosis may be made. The instillation of a mydriatic, the drinking of a large quantity of water or an injection of caffeine are some of the methods which are used.

Tonography is a relatively new method of examination which has opened a new field of study. A small weight is allowed to rest upon the eye for five minutes. This forces aqueous out of the eye and reduces the intra-ocular pressure. It has been found that the fall is less in glaucomatous eyes than in normal eyes because the drainage of aqueous is impeded. Tonography, which measures this rate of drainage of aqueous, is proving a valuable aid in the diagnosis and study of glaucoma.

All the foregoing methods of diagnosis involve the use of tonometers but there is one diagnostic symptom for which general physicians should be

on the look out. Nearly 90% of all cases of narrow angle glaucoma and 11% of those with wide angle glaucoma give a history of seeing halos on occasions in the evenings. The intra-ocular tension in the normal person rises towards evening and in a person with glaucoma it is liable to rise considerably above normal. A high intra-ocular tension causes corneal oedema so that on looking at a light, diffraction occurs and a rainbow-like halo is seen around it. This may be seen for but a short time and elderly folk seldom volunteer the information. It is often necessary to question the patient specifically as to whether he has actually seen a halo in the evening around a street light or a car head light.

A useful gadget has recently been introduced which consists of lycopodium powder sprinkled between two thin plates of glass. The patient is asked to look through it at a light and halos similar to those seen in glaucoma at once appear around it. This is much simpler than attempting to describe a glaucoma halo to the patient. This little accessory is cheap and can easily be kept in the desk drawer of every physician.

c) New Methods of Treatment

Diamox in the Treatment of Glaucoma

Diamox causes diuresis by inhibiting carbonic anhydrase and it also reduces the intra-ocular tension. Whilst the kidneys quickly develop a resistance to its diuretic action, its hypotensive effect on the intra-ocular pressure appears to be more persistent. The manner in which it reduces tension is not fully understood but it appears to act by decreasing the production of aqueous by the ciliary body.

When diamox was found to reduce the intra-ocular tension it was hailed as a great advance in the treatment of glaucoma. Increasing experience, however, has tempered the early optimism and, whilst there is no doubt that it is of value, its precise indications and limitations have still to be clearly defined.

In the long-term treatment of glaucoma diamox appears to be of some use especially in those patients showing decompensation despite intensive miotic therapy. A few patients find the side effects such as loss of appetite, diuresis and paraesthesiae of the legs and arms somewhat distressing and they decline to continue its use. Rarely urticarial rashes may occur.

Its chief value is in the treatment of glaucomatous states for short periods. Diamox appears to assist the effect of miotics in the treatment of acute closed angle glaucoma, but, although these measures may restore the intra-ocular pressure to normal, it is always advisable to perform an iridectomy to prevent another attack.

It is also of value in controlling the intra-ocular tension in secondary glaucoma due to inflammation or injury. In some cases the reduction in tension relieves pain and prevents damage to vision until the primary condition subsides. In others it makes surgery safer and more effective.

Miotics such as pilocarpine, eserine, and doryl remain the chief form of treatment in chronic glaucoma. If these fail to maintain the intra-ocular tension at safe levels, surgery is required. The surgical procedures in common use at the present time are still those which were introduced before the first world war. Only diathermy to the ciliary body, which appears to act by decreasing the production of aqueous, has any claim to being a recent innovation and its value is not yet established.

Treatment of Convergent Squint

It has long been known that most convergent squints are associated with hypermetropia. Accommodation and convergence are yoked actions. When a young child with hypermetropia begins to take interest in near objects the excessive accommodation which is required to overcome the hypermetropia tends to cause over-convergence and result in a convergent squint. It is customary to give these little patients the full correction for hypermetropia measured under atropine cycloplegia to relax accommodation and the associated convergence. A convergent squint which is corrected or reduced in degree by this method is known as an accommodative squint.

A common feature of this type of squint is intermittence, the squinting eye tending to swing in when the child is tired, conscious of being observed, or is looking at near objects. In the past mydriatics such as atropine or homatropine were often used to paralyze accommodation in the hope that convergence would also relax.

When, a year or so ago, it was suggested that a strong miotic, D.F P.* should be used to produce spasm of accommodation in intermittent accommodative convergent squints it was greeted with scepticism. It is given in order to cause peripheral stimulation of accommodation. Convergence is not similarly stimulated because the yoking of the two functions is central. This method has not been generally accepted but many ophthalmologists are enthusiastic about its value.

An interesting complication which may arise from the use of D.F.P. is the development of cysts of the iris pigment epithelium in the pupil. However, it appears to be of little significance and the cysts disappear when the drug is stopped. At a recent meeting Parks stated in Chicago that he had treated over 100 such cases without seeing any large pigment cysts. He thought they were caused

*Described by John Foster of Leeds and produced by Rayner, London, England.

*Di-Isopropyl Fluorophosphate (Floropryl) Merck and Co. Inc.

by the excessive administration of the miotic and could be avoided by using weaker concentrations. He strongly recommended its use. It seems that in the not too distant future D.F.P. will have an established place in the management of squint.

Intra-ocular Acrylic Lenses

In 1951 Ridley of London, England first described his method of removing the cataractous lens from the eye and replacing it with an acrylic one inserted between the iris and the posterior lens capsule. This innovation was as revolutionary as Daviel's introduction of cataract extraction in 1752.

Ridley has continued to use this method with increasing success and confidence and recently he reported upon a series of more than a hundred cases. Since then reports upon the use of Ridley's operation have appeared from all over the world. Some are favorable and some are not. At a recent Cataract Panel of the American Academy of Ophthalmology and Otolaryngology the consensus was that its value was not yet sufficiently proved to justify its general adoption.

Ridley's operation is indicated particularly in young patients with uniocular mature cataracts. It is essential, however, to perform an extracapsular extraction when an acrylic lens is to be inserted into the eye and cataracts suitable for this type of extraction are not common in young people. Moreover, the average cataract patient requires surgery at a time when the cataract is still immature and an extracapsular extraction is contraindicated. An immature cataract should be removed by the intracapsular operation.

Whatever the final appraisal may be, Ridley's method has opened a new avenue for investigation. Professor Bietti of Parma, Italy has more recently devised an operation in which the acrylic lens is placed in front of the iris instead of behind it as in Ridley's operation. These newer methods of dealing with cataract are still in the early experimental stages and we await future developments and assessments of results with great interest.

Corneal Grafting or Keratoplasty

Although little new in this subject has emerged during the last few years it is desirable to mention the present position in this field for two reasons. In the first place the Eye, Ear, Nose and Throat Section of the Manitoba Medical Society has made arrangements at both the Winnipeg General Hospital and St. Boniface Hospital for a supply of donor material should a corneal graft be required. Secondly there is some misunderstanding concerning the indications for grafting and the value of the procedure.

Indications

1. Therapeutic

The transplantation of a thin layer of cornea has considerable therapeutic possibilities. French ophthalmologists have shown that recurrent or chronic corneal ulceration and inflammation often subside after a lamellar graft and the optical results are very little inferior to those of the full thickness graft.

2. Optical

An optical graft is indicated only in an otherwise healthy eye with an opaque scarred cornea which reduces its vision to less than 6/60 or 20/200.

It should be realized that the results of the operation of corneal grafting are by no means always successful. Probably only 10% regain vision of 20/30, 70% or so are improved but 30% of patients may actually have poorer vision after operation. It is therefore necessary to do a corneal graft only if the vision is already so bad that it cannot be made much worse. Careful assessment of both eyes is therefore required and the risks should be discussed frankly with the patient.

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1950	1952	1954	1955
Cortone*	Hydrocortone*	Alflorone*	Deltra*

'Hydeltra'

2.5 mg.-5 mg.
(scored)

'Hydeltra' Indications:

'Hydeltra'

'Hydeltra'

SHARP & DOHME

Anaesthesiology

A Review of Induced Hypotension

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The introduction into anaesthesia and surgery of controlled hypotension has brought to the patient many advantages which for the most part cannot be obtained otherwise. Surgical haemorrhage can be so reduced that controlled hypotension, when it is indicated, affects not only the success of the operation, but the chance of survival of the patient.

Induced hypotension is essentially a refinement designed to provide better and safer surgery. There are very few operations where it is indispensable. It is unnecessary and unjustified for the majority of cases; it demands constant care and attention as well as considerable practice and clinical judgment in order to achieve safely the improved operative conditions made possible by this method. Safety for the patient is the prime consideration and depends upon the skill of both anaesthetist and surgeon and their mutual co operation.

Before discussing the various methods in use, it is well to consider the physiological basis of induced hypotension and compare it with oligaemic shock.

Physiology of Induced Hypotension

When there is a sudden loss of blood volume, the body acts by metarteriolar constriction in areas which are not vital to survival concomitant with vasodilation in more vital areas. An attempt is made in this way to adjust the vascular tree to the available blood volume, and so to maintain a near normal haemodynamic system. Following blood loss, fluid from the interstitial spaces moves into the blood stream to bolster the diminished circulating volume. Tachycardia develops in order to supply the vital tissues with sufficient blood and oxygen. If treatment does not soon succeed to re-establish an adequate blood volume, all these compensatory mechanisms will fail. Vasoconstriction will give way to dilation, followed by peripheral congestion and stasis. Tissue hypoxia then develops with its potentially lethal sequelae unless the process can be rapidly reversed.

Controlled hypotension whether by spinal or epidural anaesthesia, or by the systemic administration of drugs, is brought about by a different mechanism from the one described. Here vasoconstrictor impulses are blocked, thus from the onset giving rise to vasodilatation rather than constriction. Blood pressure falls because of the increased vascular area. Blood volume is normal, circulation remains adequate, tachycardia does not occur, venous return is good, and cardiac output is essentially undisturbed. Tissue hypoxia does not develop as long as adequate oxygenation is maintained. Brain damage will not occur with controlled hypotension when used by experienced anaesthetists, provided a safe blood pressure level is maintained and the patient's head is not unduly elevated. The patient's skin must be dry and warm with dilated superficial veins and capillary refill time must remain normal. Air hunger, denoting hypoxia, cannot be tolerated at any time. The degree of hypotension should be controlled at a safe level for each patient. Different patients will respond in a different way to any one method. A systolic blood pressure of 65 - 80 mm. Hg. would seem to be a safe level in an otherwise normotensive individual. However, blood pressure is always kept at the highest possible level which will give the desired optimal operating conditions at any given time.

Methods

Arteriotomy

Gardiner in 1946[1] described his method of controlling bleeding by arteriotomy. Blood is withdrawn usually from the radial artery until blood pressure has fallen to approximately 80 mm. Hg. in the healthy normotensive patient. Reduction of bleeding can thus be achieved and further falls in blood pressure corrected by replacing suitable quantities of the withdrawn blood by intra-arterial infusion. At the end of operation, blood is reinfused until the blood pressure returns to its normal level. This method approaches a pre-shock level as it utilizes blood loss to achieve diminished bleeding and, therefore, the safety margin is small.

Spinal Anaesthesia

In 1948, Griffiths and Gillies[2] used a high spinal block to induce hypotension. The technique proved satisfactory and they said that a pressure of 60 mm. Hg. systolic was adequate for tissue metabolism and cellular respiration. Gillies first introduced the term "controlled circulation" in his Clover Lecture in 1950.[3] The essential feature of the total spinal technique is a block of the autonomic outflow from the spinal cord. This can also be achieved by an epidural injection without any of the potential complications which have been described following subarachnoid injection.[4] Bradycardia is usually observed with these techniques. Green[5] has drawn attention to the fact that only a high sympathetic spinal anaesthetic is required, which not necessarily need affect many somatic segments. This he has termed "hypotensive spinal". Because of the high degree of

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technical skill required and because of its lack of flexibility, hypotensive spinal has remained of limited application.

Methonium Compounds

Pentamethonium and Hexamethonium paralyze the autonomic ganglia, thereby producing a fall in blood pressure. Their use was developed in an attempt to avoid the disadvantages and some of the specific contra-indications of the spinal technique. The methonium compounds have been used widely, but their use is accompanied by a number of disadvantages. They will reduce blood pressure but do not enable it to be quickly raised or lowered as desired. After the initial fall, it is often hard to control a rising blood pressure speedily and on demand. In young people, tachyphylaxis develops rapidly and thus resistance develops to further doses of the methonium drugs. In others, even the initial dose response varies widely. To some extent this difficulty can be overcome by the use of intravenous procaine amide[6] in association with them or by a small single injection of Arfonad.

Pentolinium Tartrate (Ansolysen)

The duration of action of this ganglionic blocking agent is greater than that of the methonium compounds. The initial fall of blood pressure is relatively slow. There is no sudden drop as is often seen with the methonium compounds. The fall of blood pressure, although slower, continues longer and may take 10 - 15 minutes to stabilize with the patient in the horizontal position. A steady level of hypotension for about 40 minutes may follow a single injection of this drug. It rarely causes tachycardia. Its main disadvantage is that blood pressure cannot be rapidly returned to normal when desired unless vasopressor agents are used. Hypotension tends to be fixed at a certain level rather than be flexible, similar to methonium induced hypotension.

Trimethaphan Camphorsulfonate (Arfonad)

Arfonad has a rapid onset of action and is of short duration; therefore it is usually administered by continuous intravenous infusion.[8] If only a very short period of hypotension is required, it is possible to provide a safe level of blood pressure and a good operative field by giving Arfonad as a single intravenous injection[9]. The continuous infusion of Arfonad will allow the gradual lowering of blood pressure to any desired level and will then permit this level to be altered upwards and downwards on a minute to minute basis. In the great majority of cases a good control of blood pressure can be maintained. The number of successful cases using Arfonad for controlled blood pressure is greater than with any other known technique, and controllability increases with depth of anaesthesia. The level of blood pressure can always be adjusted from moment to moment in close response to the varying surgical needs. Similar to the methonium compounds, procaine hydrochloride and procaine amide will potentiate the action of Arfonad, but at the same time they diminish the ready reversibility of hypotension. When the administration of Arfonad is stopped, the blood pressure usually starts to rise within 3 - 10 minutes, depending on the amount of drug given and the depth and duration of anaesthesia. No real changes can be demonstrated in venous pressure, electrocardiograms or electroencephalograms when the blood pressure is gradually lowered with this drug. Continuous administration of this drug over a long period and on repeated occasions has not produced any untoward effects.

Physical Aids

The use of posture has been advocated by the early users of the ganglionic blocking agents as an essential part of the technique for induced hypotension.

Posture may be used with induced hypotension when the head and neck are dependent without fear of cerebral complications. The use of the headup tilt during hypotension, however, must be used with great care, as cerebral oxygenation may be impaired, depending upon the degree of hypotension and the state of the cardio-vascular system.

Some feel that the headup tilt is needed in operations on the head, neck, and chest wall, but in actual fact it is rarely necessary to exceed 5°, and should never be more than 15°. If such elevation of the head is desired an additional safety factor may be provided by lowering body temperature.

Hypotension is induced slowly with the patient in the horizontal position. If it has been decided that headup tilt is desirable, systolic blood pressure is stabilized at a higher level, e.g. 85 - 90 mm. Hg. in a normotensive individual; after elevation of the head there will be then a further fall in blood pressure. A short acting agent should be used, so that, if excessive fall of blood pressure should occur, the infusion can be stopped, and the patient returned to the horizontal position or head down tilt until there is a return of adequate blood pressure. In the absence of significant elevation of the head for intracranial operations, bleeding will still occur, but haemostasis is markedly facilitated. We advocate this as a compromise between two extremes as it will add greatly to the safety of the procedure.

Saunders[10] has described a negative pressure device which can be applied to the patient's legs in order to lower the blood pressure. Hypotension is induced with any of the ganglionic blocking drugs and the blood pressure can be further lowered without more drug being given by applying pneumatic suction to the legs. This technique has proved useful when a steady low level of blood pressure is required to assist in the complete removal of large vascular masses, as for

example, haemangiomata, meningiomata and cerebral aneurysms. From personal experiences the pneumatic device has proven a useful adjunct to the methonium compounds and eliminates the need for posture; it is not needed with Arfonad.

Indications and Contra-Indications

These are the same for any of the drugs described.

Indications

1. **Neurosurgery:** "Vascular brain tumours and cerebro-vascular aneurysms." Reduced bleeding may render operable an otherwise inoperable tumour. Hypotension causes some shrinking of the brain and so improves exposure at the site of operation. Cerebrovascular aneurysms are softer and less friable with hypotension.

2. **Large Vessel Surgery:** "Operations for arteriovenous fistula, excision of coarctation of the aorta with or without grafting, anastomosis of other large blood vessels and arterial grafting." Anastomosis of large vessels is greatly facilitated. Under hypotension the coarcted aorta resembles a velvet tube. The anastomosis is made easier technically and the line of anastomosis is not subjected to a sudden rise in pressure when the clamps are removed. A short, thin-walled patent ductus arteriosus may be ligated or divided with less risk of being torn when clamps are applied.

3. **Operations Associated With Great Blood Loss:** "Complete pelvic clearance for neoplasm" or "block dissection of the neck with hemisection of the mandible" are benefited by the diminished blood loss and by the drier field. "Spleno-renal shunts", "porto-caval anastomosis", and the "Whipple operation" are also much facilitated.

4. **Inability to replace blood** in amounts that would be required if no hypotension were used. Unusual blood groups may be an indication for hypotension in order that the small supply of blood available may suffice for the procedure at hand.

5. **When the Presence of Bleeding would Endanger the Success of Operation:** The fenestration operation, major plastic surgery to face, head, and neck come under this heading.

6. **Treatment of Pulmonary Oedema** of Cardiac Origin[10].

7. **Control of Severe Systemic Hypertension.**

8. **Conservation of Time:** This only constitutes an indication on very rare occasions where time is of the essence.

Contra-Indications

1. Arteriosclerosis.
2. Severe cardiac disease.
3. Shock.
4. Severe visceral disease, e.g. liver or kidney.
5. Hypovolaemia.
6. Uncorrected anaemia.
7. Degenerative disease of the central nervous system.
8. Inadequate fluids available.
9. Inability to replace blood loss which may be needed while hypotension is being used.
10. Inadequate skill on the part of the anaesthetist.

Other Considerations

The benefits of hypotension have enabled a dramatic forward step in certain fields of surgery. If it is the considered opinion of the surgeon that any particular operation can be performed equally well and with as great a chance of success without hypotension, then it should not be used. Controlled hypotension should never be employed by the inexperienced or inattentive, and it can never be recommended for indiscriminate use. The use of controlled hypotension is dictated solely by the patient's needs.

The anaesthetist must be fully prepared for the hypotensive technique before the start of the operation. Hypotension should not be started during an operation to control bleeding, if blood loss exceeds expectations, until all blood lost has been replaced. By the time this has been achieved, the indications for controlled hypotension may well have passed. Whatever blood is lost during controlled hypotension must be replaced assiduously, lest more severe and intractable oligaemic shock supervene. Repeated administration of ganglionic blocking drugs at successive operations so far does not appear to be followed by obvious clinical ill effects.

It is felt by many surgeons and anaesthetists, that patients who have had controlled hypotension during surgery are in a better condition after operation than they would have been without it; this seems to indicate that autonomic blockade in some way protects from traumatic shock.

Conclusions

After some years of practical experience, controlled hypotension may be said to have passed beyond the experimental stage. With the introduction of Arfonad, an agent is available which allows for reliable and quickly adjustable control of blood pressure levels. Indications and contra-indications have been worked out, and it is interesting to note that only in relatively rare instances the method is really indicated. The ultimate criterion is the benefit derived by the patient, either because an otherwise inoperable condition is made operable, or because the chances of success are greatly enhanced by the use of the method. Never should hypotension be induced for the convenience of the surgeon, or of the anaesthetist, or merely in order to save a bottle of blood. There is an increased hazard associated with the use of induced hypotension, and the risk thus taken must be justified by the benefits obtained.

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Abstracts from the Literature

The Significance of Calculus Size in Determining the Indication for Elective Cholecystectomy: C. J. Schein, E. S. Hurwitt, M. A. Rosenblatt. Gastroenterology, 29: 377, 1955 (Sept.)

Of 1,334 consecutive autopsies on patients over 50 revealed that 17% had cholelithiasis. Of those with stones, 7.5% had common duct stones. Two groups were differentiated. The first group, 22.5% of the total, had 1 or 2 large stones 2cm. or more in diameter. The second group, 77.5% of the total, had gravel or numerous stones less than 2 cm. in diameter. With the large stone(s) 67.2% had evidence of chronic cholecystitis. With small multiple stones, 23.8% had evidence of chronic cholecystitis. 85 primary gall bladder operations for stones were reviewed. Elective operations (54%) had no mortality. Emergency operations for acute obstructive cholecystitis (46%) had a mortality of 5%, and both deaths were in patients with large stones. There is an increased incidence of large stones in surgical patients, especially those with acute obstructive cholecystitis. Increased morbidity and mortality occur with solitary calculi. The risk of cholecystectomy is increased in older patients operated on as emergencies. One-third of older patients operated on for biliary tract disease as an emergency had cystic duct obstruction. Patients with one or several large stones are more likely to develop acute cystic duct obstruction or gallstone ileus, and it is felt that elective prophylactic cholecystectomy is even more strongly indicated than in patients with multiple small stones.

A. G. Rogers.

The Effect of Morphine on the Serum and Urinary Amylase and the Sphincter of Oddi: H. L. Nossel, G. Efron. Gastroenterology, 29: 409, 1955 (Sept.)

Morphine sulfate may produce serum amylase concentrations and urinary amylase values that fall in the range of values found in primary acute pancreatitis. It occurred in 2 patients of 43 with gall stones. In other observers' experience, it occurred in 6 of 41 patients. It has also been observed after codeine in 6 of 27 patients. In one case, the elevated amylase was thought to be due to the effect of morphine on the bile and pancreatic ducts. It did not occur after morphine when the fluid flowed constantly into the duodenum with infusion through a T-tube.

A. G. Rogers.

A New Early Diagnostic Sign of Phlebitis of the Lower Extremities: Ortiz-Ramirez T. and Serna-Ramirez R., Amer. Heart Journal, 50: 366, 1955 (Sept.)

The "Cuff" sign: The authors present a new test for aid in diagnosing deep vein phlebitis of the lower extremities. With the patient recumbent, the extremity to be tested is slightly flexed at hip and knee. A sphygmomanometer cuff is wrapped around the leg just above the knee and is inflated to 40 mm. Hg. A positive test is characterized by deeply localized pain in the popliteal or calf muscles. The pain appears within two to five minutes and often increases in intensity while the cuff remains inflated. The pain disappears rapidly on removing the cuff. It is felt that the test depends on the presence of an inflamed venous wall which increases the pain sensitivity of the vessel to distention of the lumen. The inflated cuff occludes venous return and thereby causes distention of the lumen distal to the cuff.

In a series of thirty-two patients with thrombophlebitis of the lower extremity, the authors found the "cuff" sign to be positive in every instance, compared with 81% for "Homans'" sign and lesser percentages for other commonly used tests for thrombophlebitis. In patients with varicose veins and other periphero-vascular diseases, the "cuff" test was found to be negative.

The "cuff" test would appear to be a simple but useful aid in the diagnosis of thrombophlebitis of the lower extremities. There is great need for such a test in cases of incipient phlebitis or where pathognomonic clinical manifestations are not present.

D. H. Stein.

Editorial

S. Vaisrub, M.D., M.R.C.P. (Lond.), F.R.C.P. (C.), F.A.C.P., Editor

The Irony of Fat

Let me have men about me that are fat . . .
Wm. Shakespeare, Julius Caesar, Act 1, Sc. 1.

W'at good eese wife, eef she don'ta be fat?
Thomas Augustine Daily, Da Styleesha Wife.

The quotations that grace this page make it clear that obesity has not always been regarded as a reprehensible trait. On the contrary, since throughout history food has seldom been plentiful, avoirdupois represented the abundant life. A fat man was a "man of substance," someone to be envied and respected; a fat woman was "pleasantly plump", the inspiration of the artist. This attitude is by no means extinct. In countries where food is scarce, overweight is synonymous with good health, and good looks. (Indeed it is an open secret in the harems of Morocco that the fat ones are the favorites of the faithful). True, physicians since the time of Hippocrates have frequently observed and recorded a higher death rate in the obese, but even they did not display anything like the lipophobia of the present day.

The attack against obesity began insidiously, and developed gradually, gathering momentum as it progressed. The first to charge (in the military sense of the word, not the financial) were the surgeons, who complained bitterly of the difficulty in getting to their targets through the thick layers of adipose tissue. They were also the first to observe the higher incidence of gall stones in the obese. "Fat, fair and forty" became a well known diagnostic refrain. Soon the physicians, following suit, began to snarl and gnash their teeth at the various chronic degenerative diseases to which the corpulent are prone. Diabetes, (diabète gras), osteoarthritis, gout and degenerative heart disease bore the brunt of the attack. It was not, however, until the Metropolitan Life Insurance Company published its statistics that the onslaught reached its present intensity. The revealed figure of some 50 per cent death rate excess for all causes in the overweight has rendered obesity indefensible.

It is only natural, in view of the prevalence of coronary disease, that its relationship to obesity would be a subject of study by many investigators. Obesity, obviously, aggravates a pre-existing coronary heart disease, as it would any other heart disease, by dint of increased demand on the cardiac output, but is it a factor in the causation of coronary atheroma?

No ready answer to this question can be given, for both coronary atheromatosis and obesity are complex processes, the former closely interwoven with cardiac dynamics and pathophysiology, and the latter with all aspects of lipid metabolism. Consequently, investigation had to proceed along many routes. Chemical analyses of atheromatous plaques, studies of plasma lipids by chemical, electrophoretic and untracentrifugal methods, animal experiments, studies of dietary habits, statistical analyses of insurance data, and other avenues of approach were tried by numerous investigators with equivocal, if not ephemeral success. The results were clear cut in some instances, but by and large they were only suggestive, the main difficulty being that of proper correlation of data, elimination of extraneous factors, and correct interpretations of findings.

Chemical analyses of the lipid content of atheromatous plaques in the coronary arteries revealed high cholesterol content in addition to phospholipids, and neutral fats. Statistical studies confirmed the clinical observation of high frequency of coronary atheroma in patients with diabetes, nephrosis, essential xanthomatosis, myxedema — conditions associated with high serum cholesterol. It was also noted that, as a group, patients, who had myocardial infarcts tended to have serum cholesterol levels somewhat higher than normal. As a result of these suggestive findings, great interest was aroused in the study of the metabolism of cholesterol, particularly the relationship of its blood levels to its content in the diet.

The results of these studies failed to reveal a definite correlation between exogenous cholesterol and that in the serum, which is not at all surprising in view of the ease with which cholesterol can be synthesized in the body. Nor did these investigations succeed in establishing a consistent relationship between serum cholesterol levels and coronary atheromatosis in all patients. Needless to say, short term trials of dietary cholesterol restriction were a therapeutic failure.

The search for a guilty liquid, however, did not end with plasma cholesterol studies. Barr and his associates have found, by electrophoretic methods a consistently elevated level of beta-lipoprotein fraction in patients with myocardial infarction. Gofman and his co-workers, using the techniques of ultra centrifugal flotation, have demonstrated in cases of coronary thrombosis a higher level of ^{S}f 10-20 and ^{S}f 30-100 than in the normal. Other simpler methods of extracting atherogenic lipids have also been reported. (P. G. Green, Manitoba Medical Review, June 1955.) This is all significant research, but what relation, if any, does it bear to obesity?

The answer to this question is not at all simple. Statistics on the subject do not lend themselves to easy analysis. Gofman and Jones found a definite

relationship between the concentration of atherogenic lipoproteins in the blood and body weight. They claim that weight reduction could prevent 17% of deaths due to coronary disease. On the other hand, studies carried out in the U.S.A. Army, reveal no significant difference in body weight between healthy men and those who had myocardial infarction. This lack of significant relationship is emphasized by A. Keys. His conclusions, based on an analysis of Life Insurance Statistics, are, that even an overoptimistic evaluation could not concede more than 2.6% reduction in mortality from coronary disease, if obesity were to be eliminated in the 55 year old age group — a very small figure, indeed.

Having, thus, eliminated overweight as the major factor in atherogenesis, have we absolved fat of all guilt? Far from it. We may ignore the fat in the body, but we must not forget the fat on the table. It is the dietary fat which is now the centre of interest. Extensive studies on the relationship between dietary fat, plasma cholesterol, and coronary atheroma are in progress in various parts of the world, studies made on a scale hitherto never attempted. Results of these investigations reveal low plasma cholesterol levels in population groups existing on a low fat diet, in contrast with higher levels in population groups habituated to a diet rich in fat. Moreover, the incidence of coronary disease appears to be much higher in the latter group. The following paragraph sums up some of the results of these investigations, reported and commented upon at the Second World Congress of Cardiology in Washington in October 1954.

Noboru Kimura of Japan, where the fat content of the diet is low, reported a low incidence of coronary disease. Only 75 in a series of 10,000, on whom autopsies were performed, died of myocardial infarction. John Higginson reported a similarly low rate of coronary thrombosis among the Bantu tribesmen of South Africa, whose diet is grossly deficient in fat. Gunnar Bjork compared the low rate of coronary disease in Finland and Norway during World War II, when fat was scarce, with the high rate after the war, when it became plentiful. He also drew attention to the differences in dietary fat and incidence of coronary disease between the prosperous population of the Southern part of Sweden and the poorer people of the Northern part. Paul White compared the incidence of myocardial infarction among general hospital admissions in Naples and Massachusetts. The frequency was nine times as high at the Massachusetts General Hospital as in Naples. Needless to say, the fat intake in Massachusetts is also much higher. The differences in the frequency of coronary atheroma between Naples and Bologna was reported and elaborated upon by Ancel Keys, who noted that the diet of the Bolognese is much richer than that of the Neapolitans, with a correspondingly higher rate of coronary disease.

The conclusion arrived at by these investigators is that there is a definite relationship between fat in the food and coronary atheromatosis. This relationship cannot, as yet, be fully assessed, for other factors e.g. exercise, occupation, living habits, must be taken into consideration. Should this relationship, however, be more clearly elucidated by further studies, it may well lead to a change in the eating habits on this continent. A return to the simpler fare of the less prosperous nations may be envisaged. In a way it would be a vindication of the views of Jean Jacques Rousseau, who believed in the superiority of the "natural" diet of the primitive savage to that of the "corrupt" civilized man. It would also demonstrate that plenty is not without its penalty, nor prosperity without its price. This is the true paradox of progress—the irony of fat.

Ed.

Letter to the Editor

Dear Editor:

In your editorial of December 1954, you don the cloak of humility and beg for "constructive criticism". Even though I am not naive enough to be taken in by your professed interest in the views of your readers, I shall nevertheless avail myself of your invitation and voice a few opinions, which may disturb your unruffled smugness.

First, I note with disapproval that too many papers, published in the Review, are presentations by visiting guest speakers. Why resort to charitable handouts from outsiders? Surely, there are enough medical writers in Manitoba to fill your pages. Why not use the same methods, whatever they may be — pleading, cajoling, coercion or blackmail, that you must have used to obtain papers from visiting dignitaries, on our local boys?

I also wish to direct some "constructively critical" remarks at your editorials. Somehow, the latter remind me of a very fat patient, who stalked into my office the other day, and, proudly displaying his obese torso, said: "Doc, here are 320 lbs., and not one ounce of it is muscle". Indeed there is very little "muscle" in your editorials. They are flabby and redundant, totally lacking in substance. You can find in them "erudite" discourses on history, philosophy, and ethics, but hardly anything pertaining to medical science. Surely, in this electrolytic era it is not too much to expect a few editorials on potassium or acid base imbalance. Nor is it unfair to demand in this age of radio isotopes, nuclear physics and vector analysis, some reference to these important subjects and their impact on medicine. Yes, even an ordinary discourse on some clinical subject would be a welcome change from the vacuous

and vaporous generalities that we have been accustomed to reading on your editorial page.

Indeed it is high time, dear editor, you rolled up your sleeves, and did some honest editorializing.

How is this for a New Year's resolution?

M. Y. Alterego.

Welfare Council Meeting

The Annual Meeting of the Welfare Council of Greater Winnipeg will this year feature a group of prominent citizens speaking on "The Community's Stake in Health and Welfare Planning." At this meeting the citizens of Greater Winnipeg will have the opportunity to hear about the developments that have taken place in the health and welfare field during 1955.

Among the reports to be presented will be the Housing Committee report, the Services for the Aged report, the Psychiatric Services report, and many others which are of interest to the citizens of our community. The meeting will begin at 8.15 p.m. and last exactly one and a half hours. "A streamlined meeting for busy people."

The meeting is to be held at the Playhouse Theatre on Thursday, January 12th, 1956. You are sincerely invited to attend.

Victorian Order of Nurses

Eighteen staff nurses of the Victorian Order of Nurses made 3,222 visits to the homes of the sick in the Greater Winnipeg area in October. The family doctors' orders were carried out during each visit. As this is written (November 22nd) the city is being blanketed with heavy snow, but the nurses are able to carry on their work. The going may be slowed down to some extent, but no one need go without adequate nursing care. Have you a post operative patient who requires a dressing or other nursing service on return home —or a maternity patient leaving hospital and a bit apprehensive of asuming the care of that brand new baby?

Obituary

Dr. Henry Funk — In Appreciation

Death came suddenly to Henry Funk, October 19, 1955.

Henry Funk would wish neither lamentation nor eulogy. Perhaps appreciation or even reminiscence by classmate, team-mate, brother, friend would be tolerated.

My first recollections of Henry were on the hockey arenas or the soccer fields. His energetic play for old Wesley against us in pre-medicine was so appreciated that we eagerly awaited that day when he would enter medicine and would hustle for us. With us he continued unselfish, rugged, but clean, athletics until our internship. Then perhaps the first faint, but grim, warnings appeared and were heeded. Since, he settled for golf (ardently), bowling, some curling and the odd duck shoot. Our last day at golf was not his best, but he shrugged it off with: "I guess a fellow of fifty can't complain too much when he shoots the eighties."

Henry's medical work is well known across Canada and the upper States. We have lost one of our better orthopedic surgeons, it is true. We have also lost a kindly physician who served many years as a country practitioner. It is not so well known however, that he was one of the first to offer his services in World War II. At enlistment he discovered an illness which, although it invalided him for months, determined his future career. He endured his rest and with grim fortitude started the long chase for his F.R.C.S.(C). Since then he qualified for his F.I.C.S. Our medical students were his friends. He taught with practical sincerity and his help extended beyond the curriculum into their private lives. That he should have been Honorary President of the students' union was a natural selection.

Sincerity, honesty, frankness were integrated in his character. Henry did not wear his emotions on his cuff, but literally lavished his affections on his wife and three young daughters. He loved and enjoyed his home and was at his best when it was filled with friends.

"That loss is common does not make
My own less bitter, rather more."

Earl Stephenson.

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vitamin-mineral combination

Prescribed early in pregnancy, NATABEC Kapseals get your patients off to a good nutritional start—help *keep* vitamin-mineral intake abreast of increased nutritional needs. NATABEC Kapseals provide iron and calcium, as well as important vitamins in a formulation expressly designed to protect the health of both mother and child.

DOSAGE: As a dietary supplement during pregnancy and lactation, one or more Kapseals daily. Available in bottles of 100 and 500.

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Medical History

"1855"

Part II

J. D. Adamson, M.D., M.R.C.P. (Ed.), F.R.C.P. (C)
Professor of Medicine, University of Manitoba,
Chief of the Department of Medicine,
Deer Lodge Hospital

About one hundred years ago some practical results from 300 years of smouldering science began to show themselves. The chief of these was a precise conception of the meaning of infection and some effective methods of combatting it. The idea of contagion was by no means new. The popular story, that Pasteur discovered organisms and Lister applied his principles to surgery and, thus, created modern surgery and man's physical salvation, is naive in all respects. The idea that some diseases are contagious goes back to the earliest history of man. Indeed, some anthropologists say it is an inherent and intuitive belief. The ancient Semites believed implicitly in contagion as is shown by the elaborate precautions prescribed to prevent the spread of leprosy, outlined in the book of Leviticus, which was written during the Babylonian captivity about 500 B.C. The most famous medical pronouncement on the matter came from Fracastor (1478-1553) of Verona, who in his work "De Contagione" (1546) definitely indicated his belief in contagiousness of syphilis. It is curious that he did not appear to have appreciated that it was essentially a venereal disease. This was possibly because it was almost a universal infection, but was undoubtedly recognized soon after. In 1686 an edition was published in London, and a prefatory poem leaves no doubt that the source of the infection was well understood by its author. He says in the classical, ornate style of the period:

Blame not the stars; tis plain it neither fell
From the distempered Heaven; nor arose from Hell.
Nor need we to the distant Indi's rome:
The curst Originals are nearer home.
Whence should that foul infectious torment flow
But from the banefull source of all our wo?
That wheedling, charming sex, that draws us in
To every punishment and every sin.

This anonymous poet was evidently speaking out of bitter experience, and his attitude is reminiscent of Adam's ungallant attitude in the Garden.

The most dramatic and tragic evidence of contagion was furnished by John Hunter, who in 1767, to prove that syphilis and gonorrhoea were the same disease, made two punctures — one on his glans and one on his prepuce—and inoculated them from a case of what he thought was gonorrhoea. He developed two chancres, and thus the two diseases were considered identical for nearly a hundred years. It seems most likely that Hunter was using a case with both infections. It is usually said that syphilis of the aorta ultimately caused his death 26 years later. However, the description of his symptoms during the last 10 years of his life, and also the autopsy, sound far more like simple coronary sclerosis.

There is an abundance of other evidence that infectiousness of some disease was well understood long before the period of which we are speaking. During the 14th Century, when Europe was devastated by plague, most countries tried to enforce quarantine laws and also practiced disinfection. In 1720 Richard Mead[1] wrote a treatise on "The Prevention of the Plague" at the command of "His Majesty's Principal Secretaries of State". Mead gives the first evidence (that I have heard) to prove the transmission of disease by the intravenous route. He says, referring to some French physicians:

"The truth is, these Physicians had engaged themselves in an Hypothesis, that the Plague was bred at Marseilles by a long Use of bad Aliment, and grew so fond of their Opinion, as not to be moved by the most convincing Evidence. And thus it mostly happens, when we indulge Conjectures instead of pursuing the true Course for making Discoveries in Nature.

"I know they imagine this their Sentiment to be abundantly confirmed from some Experiments made by Dr. Deidier upon the Bile taken from Persons dead of the Plague: which having been either poured into a Wound made on purpose in different Dogs, or injected into their veins, never failed, in many trials, to produce in them all the Symptoms of the Pestilence, even the external ones of Bubo's and Carbuncles. One Dog, upon which the Experiment succeeded, had been known, for three months before, to devour greedily the corrupted Flesh of infected Persons, and Pledgets taken off from Pestilential Ulcers, without any Injury. From thence they conclude that this Disease is not communicated by Contagion, but originally bred in the Body by the Corruption of the Bile. This corruption, they say, is the Effect of unwholesome Food; and the Bile, thus corrupted, produces a Thickness and a degree of Coagulation in the Blood, which is the Cause of the Plague; Tho' this they allow to be inforced by a bad Season of the Year, and the Terrors of Mind and Despair of the Inhabitants.

"But it does not follow from hence, that the Bile is the Seat of the Disease, or that other Humors of the Body are not corrupted as well as this. I make no question but the whole Mass of Blood is, in this Case, in a State of putrefaction; and

Medical History

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consequently that all the Liquors derived from it partake of the Taint.

"Accordingly, it appeared afterwards from some Experiments made by Dr. Couzier that not only the Blood, but even the Urine from an infected person, infused into the crural Vein of a Dog communicated the Plague. I will venture to affirm, that if, instead of Bile, Blood or Urine, the Matter of the Ulcers had been put into a Wound made in the Dog; it would have had at least an equally pernicious Effect; As may well be concluded from the Inoculation of the Small Pox."

It is a curious paradox that the first case of transmission of disease by the intravenous route was used as an argument to prove that the Plague was not contagious, but due to the "corruption of the bile"!

But none of all this really had a lasting and effective impact on practice until (according to Sudhoff)[2] "Semmelweiss and Lister became its intuitive practical interpreters and Pasteur and Koch its master investigators". This statement is, like broad historical generalizations, an oversimplification. The truth is that the practical campaign against infection was started by general practitioners in their obstetrical practice long before any of these famous men. One often sees it stated in American publications that Oliver Wendell Holmes was the first man to combat puerperal sepsis, and nearly all Europeans think that Semmelweiss began the campaign. In fact, neither of them claimed priority. In his paper "The Contagiousness of Puerperal Fever" published in 1843, Holmes makes no such claim, and goes out of his way to show that many practitioners were in the field long before that time. He gives priority to Dr. Gordon of Aberdeen who, almost 50 years earlier, (1795) produced complete evidence that the infection was carried from patient to patient by attendants, usually doctors or midwives. In true Aberdonian style, Gordon says: "This is not an assertion, but a fact, admitting of demonstration as may be seen by a perusal of the foregoing tables". The idea of infection spread rapidly, so that by 1850 all well informed obstetricians were washing their hands and wearing clean clothing; also most of them would not attend cases of erysipelas.

No doubt this obstetrical knowledge helped to stimulate the investigation of post operative infection, and this problem soon occupied the minds of surgeons in many countries. Possibly the critical circumstances in the history of infection, and the beginning of its scientific investigation was the discovery of the lactic acid bacillus in 1855 by Pasteur. Microscopic organisms had been seen before, but this was the first time in which the function was demonstrated—the first real blow to the belief in spontaneous generation. This did not produce any tangible effect in medicine for many years, and it was not until 1885 that Pasteur treated his first case of rabies. In the interval his activities had been with beer and wine fermentation, silk worm disease, anthrax in sheep and chicken cholera. But he demonstrated beyond doubt that infection, like fermentation, was due to a discoverable living organism.

Lister had commenced his investigation quite independently when he became Professor of Surgery in Glasgow in 1860. His relation to Pasteur is best shown in the opening paragraphs of his original paper entitled "On the Antiseptic Principle in the Practice of Surgery" read before the British Medical Association in Dublin in 1867:

"In the course of an extended investigation into the nature of inflammation, and the healthy and morbid conditions of the blood in relation to it, I arrived, several years ago, at the conclusion that the essential cause of suppuration in wounds is decomposition, brought about by the influence of the atmosphere upon blood or serum retained within them, and, in the case of contused wounds, upon portions of tissue destroyed by the violence of injury.

"To prevent the occurrence of suppuration, with all its attendant risks, was an object manifestly desirable; but till lately apparently unattainable since it seemed hopeless to attempt to exclude the oxygen, which was universally regarded as the agent by which putrefaction was effected. But when it had been shown by the researches of Pasteur that the septic property of the atmosphere depended, not on the oxygen or any gaseous constituent, but on minute organisms suspended in it, which owed their energy to their vitality, it occurred to me that decomposition in the injured part might be avoided without excluding the air, by applying as a dressing some material capable of destroying the life of the floating particles."

Lister first heard of Pasteur in 1865, and throughout his life continued to hold Pasteur in the highest esteem and repeatedly expressed his indebtedness,

So, we can say that modern bacteriology began with the discovery of the lactic acid bacillus in 1855. Its most immediate effect was to create a rational view of wound infections and ultimately aseptic surgery. But this effect on surgery fades into significance when we think of subsequent developments. Modern Surgery has had a dramatic popular appeal, but its accomplishments are infinitely small in comparison to the enormous saving of life from the prevention and cure of infectious diseases.

Of course, bacteriology has not had an untrammeled history. It took many years to break down the age-old belief in the atmospheric-cosmic-telluric cause of epidemic diseases, a belief that originated in Greek days and supposed that some

subtle intangible changes in the earth itself accounted for plagues and epidemics. One is reminded in the connection of Vellemin, who in 1865 produced convincing evidence that tuberculosis was infectious. No less a person than Virchow (1821-1902) laughed him out of court, and was not convinced till Koch discovered the bacillus in 1882. It evidently took Virchow a long time to recognize bacteriology. When Semmelweiss was having an uphill fight to convince the profession that puerperal sepsis was contagious, Virchow was one of his chief critics. The early death of Semmelweiss in an insane asylum has by some been attributed to this and other obstructions. It is ironical that Semmelweiss, whose chief study had been septicaemia, died of that condition (at the early age of 47).

Popular opinion, and even some medical opinion, would place the use of anaesthetics high on the list of accomplishments of 100 years ago. It has made major surgery possible and has been the means of preventing much suffering. But again it does not have a very striking effect on the total score of mortality. As in all other innovations, it was not nearly as dramatic as is usually thought. According to Osler[3] Dioscorides (40-90 A.D.) and several others in the era of Greek Medicine had fairly effective methods of producing local and general anaesthesia. In 1800 Humphrey Davy discovered the anaesthetic properties of nitrous oxide, but no one paid any particular attention. In 1844 Wells operated under nitrous oxide and soon after Long frequently used ether. Morton in 1846 made the classical demonstration with ether. There was much argument among supporters of these three over the matter of priority, but Sir William Osler insists that Morton should be given the credit, because, as a result of his work, it became, not an occasional spectacular feat, but a world wide procedure. Soon after Morton's publication in October 1846, ether anaesthesia was being used in every civilized country. Liston used it in University College Hospital in December 21st, 1846. In the same year, J. Y. Simpson (1811-1870) of Edinburgh began to administer chloroform in obstetrical and gynecological cases.

Next in importance to the beginning of bacteriology, the period of 100 years ago must be remembered because it saw the beginning of scientific experimental physiology as we know it. Up to this time, physiologists were really physicians, anatomists or pathologists who speculated upon function. William Harvey is said to be the first English physiologist, and since he visualized cardio vascular function, we are liable to think of him as a physician. But in his own day he was recognized as an anatomist, though he was a medical practitioner and incidentally also planned a book on morbid anatomy. John Hunter also is said to have been the first physiologist, though it is doubtful if he ever used the word. He was essentially a comparative anatomist and surgeon; he gave some thought to function, but actually did very little original work along these lines.

During the last half of the 18th century much of the chemistry of respiration had been worked out by Priestly (1733-1804), Lavoisier (1743-94) and others. Priestly thought that combustion produced a substance which he called "phlogiston". When the air became "phlogistigated" it could no longer support combustion. Lavoisier discovered that combustion, actually, used something from the air. He finally discovered oxygen and saw its true relationship to combustion and to respiration. This early work on combustion and respiration, I suppose, should be regarded as the beginning of modern physiology.

In 1855 there was possibly the most brilliant constellation of physiological stars that we shall ever know. In England, Sharpey was in his prime (age 53); Muller in Germany was only one year younger; Helmholtz was 34 and Ludwig was 39. Magendie in France died in that year (age 72), but Claude Bernard at the age of 32 was already beginning to surpass him. From among all these truly great physiologists it is difficult to determine which most deserves to be remembered. These are some of their most significant contributions.

Herman von Helmholtz (1821-1894) showed that the energy of living bodies is derived from combustion of ingested food and from no inherent source. He thus laid to rest the turbulent "spirits" which had haunted and bedevilled physiological thinking since the days of Pythagoras. This was the cornerstone of biological chemistry.

Carl Ludwig (1816-1895) whose text-book was published in 1856, is alleged by many to have been the greatest teacher of physiology that ever lived. He published very little original work except his text book, but he stimulated an enormous amount of research, much of which was made possible by his recording manometer.

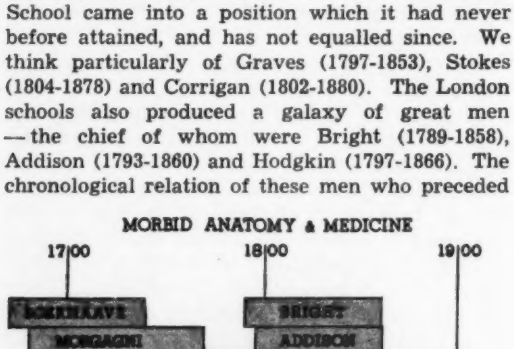
Claude Bernard (1813-1878) was possibly the greatest of all physiologists. He raised physiology to the dignity of a separate science and he insisted that it should be cultivated for its own sake. His most significant work was done almost precisely one hundred years ago. His classical publications on the gastric juice, liver function and pancreatic function all came between 1843 and 1857. The demonstration of the glycogenic function of the liver may be said to have been his most important contribution.

Possibly the most famous series of great men was to be found in Paris from 1800-1900. They were:

Laennec	1781-1826
Megendie	1782-1855
Claude Bernard	1814-1878
Brown Sequard	1817-1894

These four dominated scientific Medicine in France for nearly one hundred years. They were anatomists, pathologists, physiologists and physicians and occupied various chairs in several institutions before the days when these specialties were sharply defined as they now are.

Immediately following this, and partly overlapping these striking advances in physiology, men began to apply themselves to the practical problems of sick people in a scientific way. We remember this period of one hundred years ago by the British Schools, but of course a similar activity was present in Germany and France. The Dublin School came into a position which it had never before attained, and has not equalled since. We think particularly of Graves (1797-1853), Stokes (1804-1878) and Corrigan (1802-1880). The London schools also produced a galaxy of great men — the chief of whom were Bright (1789-1858), Addison (1793-1860) and Hodgkin (1797-1866). The chronological relation of these men who preceded



and succeeded them is shown in the chart. It is only fair to say that these men owed much of their inspiration to the French school which preceded them, especially Bichat (1771-1801), Corvisart (1775-1821) and Laennec (1781-1826). All of these men, French, Irish and English, were essentially morbid anatomists who spent their lives correlating what they found at autopsy with clinical signs and symptoms. This great age of medicine was crowned and in a sense terminated by Koch (1843-1910) and Osler (1849-1920).

But an account of the general medical advances of the past 100 years would be incomplete without a word about the humanitarian side. We might say that the baby who was born one hundred years ago was nourished on the milk of human kindness. This is illustrated in particular by the growth of hospitals. Up to one hundred years ago they were largely operated by poorly supported charities and used only for the poor, the destitute, and the hopeless. Because of poor nursing and medical care, the mortality rate was very high, and hospitals were commonly regarded as charnel-houses where people went to die. Some of our older patients are still stricken with horror when it is suggested that they go into hospital, because of the memory of those days. Up to 1700 there were only two real hospitals in the British Isles, St. Bartholomew's and St. Thomas'. In the following 150 years, when a great flood of philanthropy swept the country about two hundred hospitals were founded. The first "cottage" hospital came in 1859. Up to this time hospitals were nominally purely charity institutions. D'Arcy Power[4] makes some interesting comments on hospitals of one hundred years ago:

"Although admission to the general hospitals was theoretically free to the poor, it was in fact so hedged round by restrictions as to render it almost impossible for a poor man. At St. Bartholomew's Hospital a patient had first to obtain a Governor's letter, which was necessary even in the most urgent cases, or he had to deposit a sum of nineteen shillings and sixpence for burial fees, which, of course, was returned if he were fortunate enough to recover. If he died, the beadle had to be paid one shilling for giving a death certificate, the bearers were paid two shillings for carrying the body as far as the hospital gate. A shilling was due to the matron for the use of a pall, and the stewart was paid a shilling for certifying that the patient had died. The scandal of these payments, at last, became so flagrant that the whole system was swept away and easier means of access became universal. By a coincidence, the reform originated with a student at the very hospital in which the abuse had been most rife. William Marsden, a pupil of John Abernethy, was going home one bitterly cold night in 1828 when he found a girl of eighteen nearly dead of disease and starvation lying on the steps of St. Andrew's Church. She had been refused admission to St. Bartholomew's Hospital, hardly a stone's throw away, because she had neither money nor a Governor's letter. He took care of her, started an agitation which led to the foundation of what is now "The Royal Free Hospital", and so abolished the whole iniquitous system".

The nursing profession is almost entirely a product of the past hundred years. Before that time nurses were drawn from the lower strata of society; they required no education and received no formal training.

There is no doubt that Florence Nightingale was largely responsible for the beginning of

improvement, both in nursing and in hospital administration. She lived for 90 years (1820-1910) and spent the last sixty years of it in a vigorous and vituperative fight to reform hospitals and nursing. Her main campaign commenced after gruelling experience with a completely incompetent medical service in the Crimea—almost exactly one hundred years ago now. During the last fifty years of her life she was a confirmed invalid. She rarely moved from her bed or couch, and frequently threatened to die when she was crossed. In her later years she became fat and mellow. She had money, political influence and unending pertinacity and courage, and lived to see nursing established as a respected and respectable vocation.

In speaking of hospitals, it is of interest to note that the first tuberculosis sanatorium was opened in 1855 by Herman Brehmer in Silesia. The principles that led to its origin were, according to our ideas, quite wrong. Brehmer thought that a high altitude and mountain climbing would increase pulmonary ventilation and thus cure the lung. However, the idea of segregating tuberculosis in a special institution originated with Brehmer and spread throughout the world. Curiously enough, the first sanatorium started by Trudeau in the Adirondacks in 1885 closed its doors exactly one hundred years after Brehmer, largely because the treatment of tuberculosis has been so successful that fewer beds were required.

The whole plan of medical education and licensure has been reconstructed in the past hundred years. Before that time, in most countries, the profession was not organized as a unit. There was a multitude of methods by which one could become a practitioner. The apprentice system still prevailed to a large extent. By this method, boys (often with little education) became bottle-washers, messengers, and servants to practitioners; in the course of months or years they gradually assumed the responsibility of general practice, which consisted largely of compounding a multitude of complex mixtures and applying the depletion methods of treatment to all and sundry. After a certain number of years a license of a sort could be procured in some countries; but this was not stringently insisted upon, and it seems certain that most of those who lived by the care of the sick had been educated in this haphazard way, or indeed not trained in any way. In contrast to this "practical" method of becoming a "doctor", there was the highly elaborate academic method. This consisted of a long period in Oxford or Cambridge in the study of the ancient medical lore (Greek and Arabian) philosophy, logic, astronomy, and mathematics. After that, the students usually spent some years at one of the well established medical schools on the continent, (Padua, Bologna and Leyden were popular). This method produced a highly erudite physician who could glibly recite in Latin all the theories in medicine from Hippocrates and Galen to Rhazes and Avicenna, but one wonders whether he actually treated patients more effectively than the lad who had had his education in the field.

In Britain the reform of Medical Licensure was really begun by the profession with the establishment of the British Medical Association in 1832. In effect, they demanded that all those who practice medicine should be qualified in the three branches — Medicine, Surgery and Midwifery and that the state should take action against those who practiced without such qualifications. It required fifty-four years of continual conflict in the profession and in Parliament before these principles were finally recognized by the Medical Act of 1886. This Act is the model on which licensure in this Continent has been modeled. It has done much to protect sick people from the charlatans and to elevate the standards of medical practice among those alleged to be qualified.

At the beginning I said that I should be pragmatic and try to show how medicine, one hundred years ago, began to make significant contributions to the immediate welfare of mankind. I have referred to a few important details which in themselves must have had a direct effect. But, important as these are, they are only details. They were really by-products of something infinitely more profound that was taking place in all civilized society one hundred years ago; and this deep undercurrent was reflected not only in Medicine but in every other human activity. The genesis of this movement, of course, has been the subject of the life-long study of our best historians. We can only say that with the invention of printing, the improvement of intercommunication and the consequent spread of information, mankind began to realize that living could be made less grim by social consciousness and control. In England this was particularly manifested in the industrial revolution, the class emancipation, the freedom of the press, and the general improvement and liberalization in educational systems. In medicine it showed itself, particularly in 1848, with the Public Health Act in Great Britain. This, like other reforms, was one of the visible culminations of the centuries of tentative groping that had gone before.

Sir George Newman[5] speaking in 1925 summarized the origin of Public Health in England as follows:

"... So, first among the forces which produced public health reform must be placed the democratic and social aspiration of the people.

"This aspiration had its source in discontent and alarm. The English people became discontented with the disease and despair which followed the train of the industrial revolution, with grinding poverty, with the labour exploitation of women

and children, and, after the middle of the century, with the cruelty and waste of the Crimean War; and they became alarmed at the ravages of the cholera and of small-pox. It was Chadwick's monumental 'survey' into the sanitary condition of the people in 1842, his magnum opus, which led to the Royal Commission on the health of the towns, and ultimately the Public Health Act of 1848. This last effort of Chadwick had its source in his work, first as a Poor Law Commissioner, and then as Secretary of the Poor Law Commisssion. Our public health service is the direct offspring of the original Poor Law Service, and sprang out of the fuller appreciation of the close relationship between the life and occupation of the poor, and their disease and early mortality. Such was the ground of their discontent. But alarm also played its part. For the ravages of cholera in its four principal invasions of this country in 1831, 1848, 1853 and 1866, had proved a solemn warning to all men that, unless greater attention was given to sanitation, the country was unsafe. This feeling was increased by the epidemic of small-pox in 1871-1872".

In the actual practice of medicine, possibly the greatest change in the interest of patients that was occurring one hundred years ago was negative rather than positive. It was the renunciation of the depletion method of treatment that had prevailed almost universally since the first days of recorded history.

The story of phlebotomy is one of the most interesting and amazing chapters in human history. It had its origin before Hippocrates and remained almost unchallenged in the treatment of nearly all diseases right up to our own day. It was also used as a prophylactic. It originated in the fundamental belief that disease was due to faulty adjustment of the humours in the body. The blood itself was regarded almost as an excretion, and had to be removed in order to cure the "corruption". The revolution against this savage practice started as far back as Morgagni.

One of the first medical men of repute to protest against this was Magendie in 1841. Claude Bernard gives an account of a medical meeting at which a paper was given which "proved statistically" that bleeding is the best treatment for pneumonia. Magendie protested that his patients did just as well without phlebotomy. One of his friends — a colleague — could not restrain a smile and said "You do not bleed your patients, it is true, but your internes bleed them behind your back".

Bernard goes on to say "The next morning Magendie complained bitterly to me of this violation of his orders, and I must say after that no more patients were bled." But it was a good many years before the profession at large had renounced depletion treatment — sweating, purging, leeching, cupping and bleeding. Even Osler in his first edition in 1892 is not quite emancipated from this ancient incubus.

In summary it may be said:

1. The gestation period of medicine started about 1500.

2. It was not until about one hundred years ago that this long period of submerged growth produced anything of specific benefit to the health of mankind.

3. About 1855 the baby of Modern Medicine was born and has thrived prodigiously since then.

4. Various circumstances surrounding the long history of growth have been discussed.

5. The ultimate test of the efficiency of general prophylaxis and treatment is man's survival. If we use this criterion, it shows that according to present trends, the population will have doubled from 1850 to 1950 (from 1000 to 2000 million) and will have doubled again in the next hundred years.

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Department of Health and Public Welfare

Comparisons Communicable Diseases — Manitoba (Whites and Indians)

DISEASES	1955 Oct. 9 to Nov. 5,'55	1955 Sept. 11 to Oct. 8,'55	1954 Oct. 3 to Oct. 30,'54	1954 Sept. 5 to Oct. 2,'54	Total Jan. 1 to Nov. 5,'55	Total Jan. 1 to Oct. 30,'54
Anterior Poliomyelitis	2	4	2	9	26	117
Chickenpox	84	27	136	87	1002	1510
Diphtheria	1	0	0	0	2	0
Diarrhoea and Enteritis, under 1 year	15	9	12	12	93	153
Diphtheria Carriers	0	0	0	0	2	0
Dysentery—Amoebic	0	0	0	0	0	0
Dysentery—Bacillary	3	17	0	1	28	20
Dysentery—Bacillary Carrier	0	0	0	0	0	1
Erysipelas	4	0	0	3	13	25
Encephalitis	0	0	0	1	0	5
Influenza	11	6	3	3	213	82
Measles	145	119	67	37	2309	938
Measles—German	2	1	0	0	65	14
Meningococcal Meningitis	0	0	2	6	12	24
Mumps	86	36	86	36	1034	1045
Ophthalmia Neonatorum	0	0	0	0	1	0
Puerperal Fever	0	1	1	0	1	1
Scarlet Fever	15	11	46	27	155	474
Septic Sore Throat	3	1	2	4	21	50
Smallpox	0	0	0	0	0	0
Tetanus	0	0	0	0	0	2
Trachoma	0	0	0	0	0	0
Tuberculosis	50	43	1	61	484	656
Typhoid Fever	1	5	0	0	7	3
Typhoid Paratyphoid	0	0	0	0	0	0
Typhoid Carriers	0	0	0	0	0	0
Undulant Fever	1	0	0	0	7	7
Whooping Cough	70	48	61	71	637	216
Gonorrhoea	108	114	122	103	889	1146
Syphilis	11	5	4	6	83	85
Jaundice Infectious	36	35	46	24	294	338
Tularemia	0	0	0	0	2	2

Four-Week Period October 9th to November 5th, 1955

DISEASES (White Cases Only) *Approximate population.	*828,000 Manitoba	*861,000 Saskatchewan	*2,625,000 Ontario	*2,952,000 Minnesota
Anterior Poliomyelitis	2	3	15	45
Chickenpox	84	12	667	—
Diarrhoea & Enteritis, under 1 yr.	15	5	—	—
Diphtheria	1	—	2	12
Diphtheria Carriers	—	—	—	—
Dysentery—Amoebic	—	—	—	1
Dysentery—Bacillary	3	—	11	7
Encephalitis, Infectious	—	2	1	—
Erysipelas	4	—	1	—
Influenza	11	—	17	6
Jaundice, Infectious	36	71	77	47
Measles	145	73	1169	26
German Measles	2	—	134	—
Meningitis Meningococcus	—	—	5	4
Mumps	86	3	1002	—
Ophthal. Neonat.	—	—	—	—
Puerperal Fever	—	—	—	—
Scarlet Fever	15	7	191	27
Septic Sore Throat	3	12	13	34
Smallpox	—	—	—	—
Tetanus	—	—	—	—
Trachoma	—	—	—	—
Tuberculosis	50	52	72	119
Tularaemia	—	—	—	—
Typhoid Fever	1	—	2	2
Typh. Para. Typhoid	—	—	—	—
Typhoid Carrier	—	—	—	—
Undulant Fever	1	1	2	4
Whooping Cough	70	80	257	21
Gonorrhoea	108	—	123†	—
Syphilis	11	—	26†	—

†Three weeks only.

DEATHS FROM REPORTABLE DISEASES
November, 1955

Urban—Cancer, 76; Pneumonia, Lobar (490), 4; Pneumonia (other forms), 21; Syphilis, 1; Tuberculosis, 3; Jaundice (Infectious), 1. Other deaths under 1 year, 26. Other deaths over 1 year, 276. Stillbirths, 7. Total, 415.

Rural—Cancer, 39; Innuenza, 3; Pneumonia, Lobar (490), 2; Pneumonia (other forms), 11; Tuberculosis, 4; Diarrhoea and Enteritis, 4. Other deaths under 1 year, 20. Other deaths over 1 year, 191. Stillbirths, 6. Total, 280.

Indians—Cancer, 1; Pneumonia (other forms), 3; Whooping Cough, 1; Diarrhoea and Enteritis, 1. Other deaths under 1 year, 1. Other deaths over 1 year, 10. Total, 17.

◆

Anterior Poliomyelitis has not been so prevalent in Manitoba this year. At date of writing (Nov. 30th) only 28 cases have been reported. Winnipeg has been especially fortunate with only three of these cases and none with paralysis. The disease has lost none of its virulence as the latest case reported (onset Nov. 8th) was a woman aged 28 with almost complete paralysis and requiring respirator care. No deaths of 1955 cases have been reported.

Diphtheria has been a small problem during the past month and does not show in this report. In the Cranberry Portage and The Pas area about 8 cases have been diagnosed clinically and some of them have been confirmed by culture and virulence test at the Provincial Laboratory. No deaths have occurred. It must be remembered that if swabs are to be of any value they must be taken **before** antibiotics or antitoxin are given. Source of this infection has not been traced to its source but workmen from many different places have been coming into this area and the probability is that one of them was a carrier. At the present date control appears to have been established.

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